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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07K 5/10, 7/06, A61K 37/02 — A1

(11) International Publication Number: WO 93/23424

(43) International Publication Date: 25 November 1993 (25.11.93)

(21) International Application Number: PCT/EP93/01138

(22) International Filing Date: 10 May 1993 (10.05.93)

(30) Priority data:
07/885,788 20 May 1992 (20.05.92) US
07/985,696 25 November 1992 (25.11.92) US

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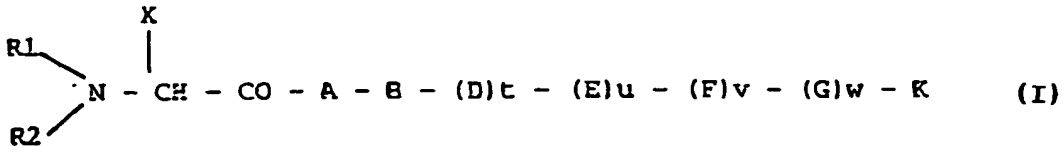
(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DERIVATIVES OF DOLASTATIN



(I)

(57) Abstract

Novel derivates of dolastatin of formula (I) in which R^1, R^2, A, B, D, E, F, G, K, X, t, u, v, and w have the meanings stated in the description, and the preparation thereof are described. The novel substances have an antineoplastic effect.

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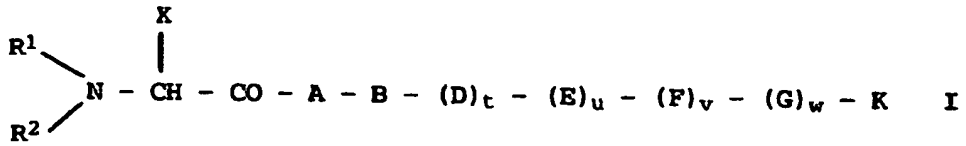
DERIVATIVES OF DOLASTATIN.

Description

The invention described herein provides novel peptides and derivatives thereof which offer potentially improved therapeutic utilities for the treatment of neoplastic diseases as compared to Dolastatin-10 and -15 (US Patent No 4,879,278, Nov. 7, 1989; US Patent No 4,816,444, Mar. 28, 1989). Furthermore, unlike dolastatin-10 and -15 which must be laboriously purified from scarce natural sources, the compounds of this invention may be conveniently synthesized as described in detail below. In addition, Dolastatin-10 is unstable to acid. It was described that even minor changes in the structure can cause complete loss of activity (Biochemical Pharmacology, vol. 40, no. 8, 1859-64, 1990).

Compounds of this invention include novel peptides of the formula I



$$R^1 \diagdown \atop R^2 \diagup \!\!> N - \underset{\displaystyle K}{\underset{|}{CH}} - CO - A - B - (D)_t - (E)_u - (F)_v - (G)_w - K \qquad I$$

where

R^1 is alkoxy, preferably C_{1-4}; alkyl, preferably C_{1-7}; cycloalkyl, preferably C_{3-6}; alkylsulfonyl, preferably C_{1-6}; fluoroalkyl, preferably fluoroethyl, difluoroethyl, trifluoroethyl, fluoroisopropyl, trifluoroisopropyl; trifluoroacetyl; amidino; ureyl; piperidinosulfonyl; morpholinosulfonyl; benzyloxycarbonyl; alkyloxycarbonyl, preferably C_{1-4}; aminosulfonyl which may be substituted by alkyl, preferably C_{1-5}; hydroxy; arylsulfonyl which may be substituted by one or more substituents independently selected from alkyl (preferably C_{1-4}), $-N(CH_3)_2$, nitro, halogen and CF_3; benzyl which may be substituted by up to three substituents independently selected from alkyl (preferably C_{1-4}), alkoxy (preferably C_{1-4}), nitro, halogen and CF_3; or NR^3R^4 where R^3 and R^4 may each be either hydrogen or alkyl, preferably C_{1-4};

R^2 is hydrogen; alkyl, preferably C_{1-4}; fluoroalkyl, preferably fluoroethyl, difluoroethyl, trifluoroethyl, fluoroisopropyl, trifluoroisopropyl; cycloalkyl, preferably C_{3-7}; acyl, preferably C_{1-8}; benzoyl or benzyl both of which may be substituted by up to three substituents independently selected from nitro, halogen, CF_3, alkyl (preferably C_{1-4}) and alkoxy (preferably C_{1-4})

R^1-N-R^2 together may be phthalimido, a 5- or 6-membered heterocycle which may be unsubstituted or substituted with one or more substituents independently selected from phenyl, benzyl, alkyl (preferably C_{1-4}), $N(CH_3)_2$, nitro, thienyl, $CONH_2$ and COOEt;

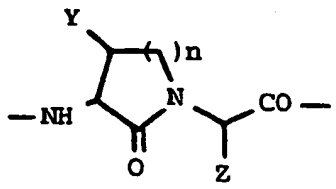
A is a valyl, isoleucyl, leucyl, allo-isoleucyl, α-aminoisobutanoyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2,4-diaminobutanoyl, ornithyl, lysyl, 2-ethylglycyl, 2-cyclohexylglycyl, lysyl or arginyl residue;

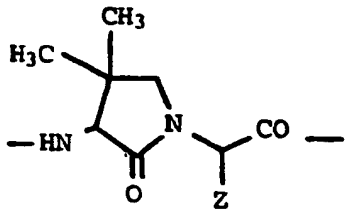
B is a N-alkyl-valyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -3-cyclohexylalanyl, -phenylalanyl, -2-ethylglycyl, -norleucyl or -2-cyclohexylglycyl residue where N-alkyl is preferably N-methyl or N-ethyl;

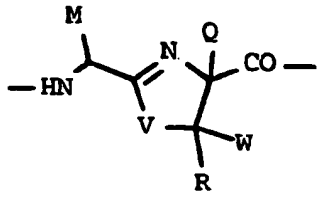
D,E,F and G are independently selected from the group consisting of prolyl, homo-prolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydroisoquinolyl-2-carbonyl, 3-thiazolylalanyl, 3-thienylalanyl, histidyl, 1-aminoindyl-1-carbonyl, 2,4-diaminobutanoyl, arginyl, 3-pyridylalanyl, 3-tert-butylalanyl, 2-cyclohexylglycyl, lysyl, norleucyl and 3-naphthylalanyl residues

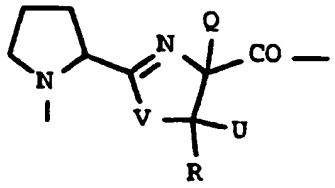
X is hydrogen, alkyl (preferably linear or branched C_{1-5}), cycloalkyl (preferably cyclohexyl), $-CH_2$-cyclohexyl or arylalkyl (preferably benzyl or phenethyl);

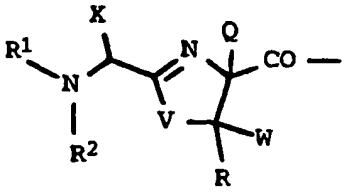
A and B together, F and G together, R^1R^2N-CHX-CO and A together, E and F together, either alone or in pairs, may be











where Y is hydrogen or lower alkyl (preferably methyl or ethyl); Z is hydrogen or lower alkyl (preferably C_{1-5}); n is 1, 2, or 3; V is oxygen or sulfur; M is hydrogen, lower alkyl (preferably C_{1-4}), arylalkyl (preferably benzyl or phenethyl), cyclohexyl, or -CH_2-cyclohexyl; Q is hydrogen; R is hydrogen or lower alkyl (preferably C_{1-3}); or R and Q may together form a bond; U is hydrogen, lower alkyl (preferably C_{1-4}), phenyl, or cycloalkyl (preferably cyclohexyl); and W is hydrogen, lower alkyl (preferably C_{1-4}) or phenyl;

t,u,v, and w are independently 0 or 1; and

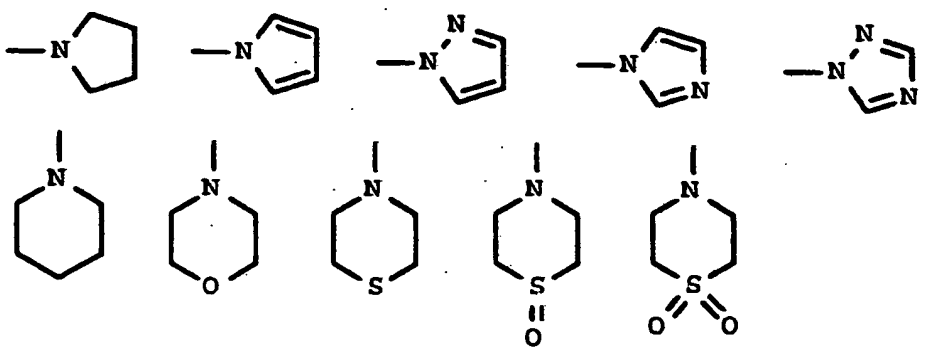
K is hydroxy, alkoxy (preferably C_{1-4}), phenoxy, benzyloxy or a substituted or unsubstituted amino moiety;

provided that where t, u, v and w are 0, K is not a hydroxy, alkoxy, benzoxy or phenoxy moiety; and further provided that where t, u and v are 0, K is not a hydroxy or alkoxy moiety;

and the salts thereof with physiologically tolerated acids.

This invention also provides methods for preparing the compounds of formula I, pharmaceutical compositions containing such compounds together with a pharmaceutically acceptable carrier and methods for using same for treating cancer in mammals.

One subclass of compounds of this invention includes compounds of formula I wherein R^1-N-R^2 is phthalimido or a 5- or 6-membered heterocycle of the formula



which may be unsubstituted or substituted with one or more substituents which may independently be selected from phenyl, benzyl, alkyl (preferably C_{1-4}), $N(CH_3)_2$, nitro, thienyl, oxo, $CONH_2$ and COOEt;

Another subclass of compounds of this invention includes compounds of formula I wherein K is an amino moiety of the formula R^5-N-R^6 wherein

R^5 is hydrogen, or hydroxy, or C_{1-7}-alkoxy, or benzyloxy, or C_{1-7}-alkyl which may be substituted by one or more fluoro atoms, or C_{3-7}-cycloalkyl, or benzyl which may be substituted by up to three substituents which may independently be CF_3, nitro, C_{1-7}-alkylsulfonyl, C_{1-4}-alkoxy, phenoxy, benzoxy, halogen or C_{1-4}-alkyl

R^6 is hydrogen, or C_{1-7}-alkyl which may be substituted by one or more fluoro atoms, or C_{3-7}-cycloalkyl, or phenyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl which may form a cyclic system, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl which may form a cyclic system, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
naphthyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, benzoxy, phenoxy, or C_{1-7}-alkyl-sulfonyl), or
benzhydryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl,

$CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
biphenyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
triphenylmethyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzhydrylethyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzhydrylmethyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy or C_{1-7}-alkyl-sulfonyl), or
naphthylmethyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
acenaphthyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
acenaphthylmethyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
pyridyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
picolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzothiazolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzisothiazolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzopyrazolyl (which may be substituted by up to two substi-

tuents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzoxazolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
fluorenyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
aminofluorenyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
pyrimidyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, COOEt, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl which may form a cyclic system, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
5-membered heteroaryl [which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, cyano, COOMe, COOEt, thiomethyl, thioethyl, thiophenyl, picolyl,acetyl, $-CH_2-COOEt$, $CONH_2$ CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, C_{3-4}-alkylen group forming a bicyclic system with the heterocycle, C_{1-4}-alkoxy, phenoxy, benzoxy, phenyl (which may be substituted by up to four substituents which may independently be nitro, CF_3, halogen, or C_{1-4}-alkyl), benzyl (which may be substituted by up to four substituents which may independently be nitro, CF_3, halogen, C_{1-4}-alkyl, naphthyl, C_{1-7}-alkyl-sulfonyl, phenylsulfonyl, or C_{1-4}-dialkylamino)], or
$-CHR^7$-5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, COOMe, COOEt, $COOCH(CH_3)_2$, $CONH_2$, COOBzl, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, phenyl, benzyl, naphthyl, or C_{1-7}-alkyl-sulfonyl [R^7 = hydrogen, linear or branched C_{1-5}-alkyl, benzyl; or R^7 and R^5 together form a group $-(CH_2)_3-$ or $-(CH_2)_4-$]).

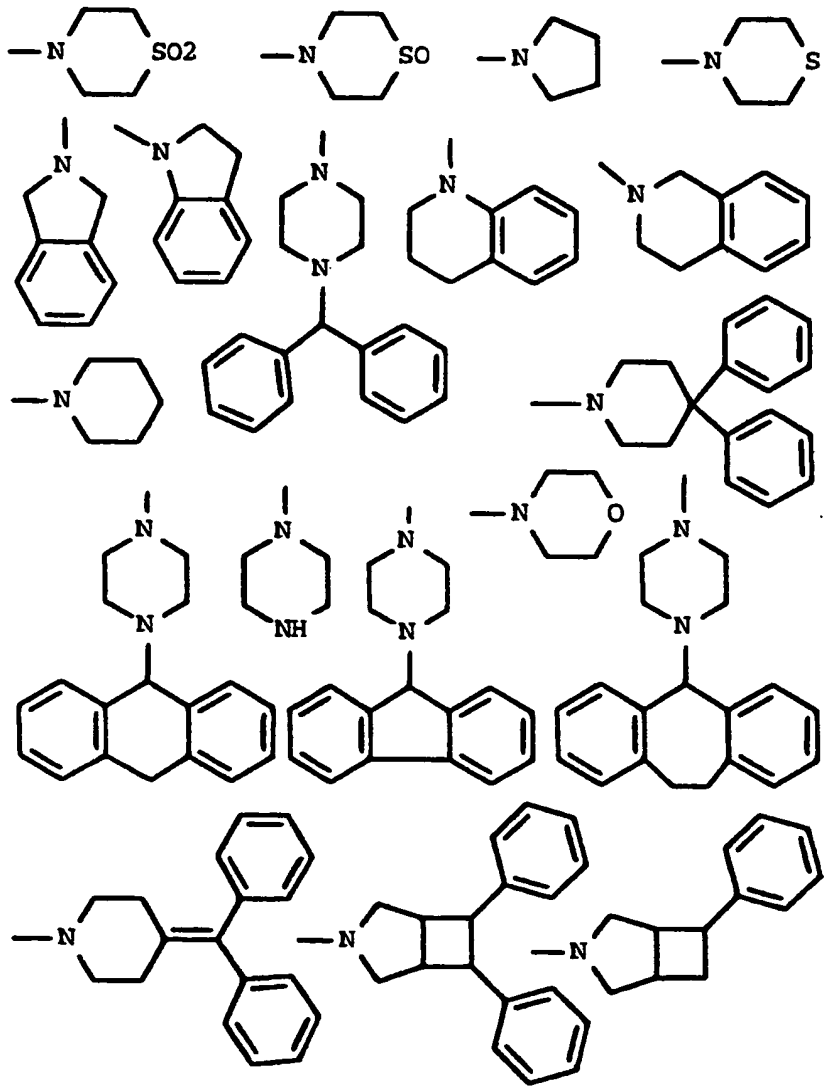
This subclass includes compounds of formula I wherein t, u, v and w are independently 0 or 1; R^1, R^2 and X are lower alkyl, A and F are lower alkyl amino acids, B is a N-loweralkylated lower alkyl amino acid; D, E, G and K are as previously defined. With the foregoing in mind, one set of such compounds can thus be depicted by the following formula II:

$R^1R^2N—CXH—CO—A—B—Pro\text{-}Pro—(F)_v—(G)_w—K$ II

and another by the following formula III

$R^1R^2N—CXH—CO—A—B—Pro—(F)_v—(G)_w—K.$ III

In another subclass of compounds of this invention $R^5\text{-}N\text{-}R^6$ together may form structures selected from the group consisting of



which may be unsubstituted or substituted with one or more substituents independently selected from the group consisting of CF_3, nitro, halogen, oxo, cyano, N,N-dimethylamino, CONHBzl, $CON(Bzl)_2$, $C_{1\text{-}6}$-alkyl, $C_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}4}$-alkylen group forming a bicyclic system with the heterocycle,

C_{1-4}-alkoxy, phenoxy, benzoxy, naphthyl, pyrimidyl, COOEt, COOBzl, C_{3-6}-cycloalkyl, pyrolidinyl, piperidinyl, thienyl, pyrolyl, $-CH_2-CO-NCH(CH_3)_2$, $-CH_2-CO-N(CH_2)_4$, $-CH_2-CO-N(CH_2)_4O$, benzyl (which may be substituted by up to three substituents independently selected from the group consisting of nitro, halogen, CF_3, thiomethyl or the corresponding sulfoxide or sulfone, thioethyl or the corresponding sulfoxide or sulfone, C_{1-4}-alkyl, and C_{1-4}-alkoxy), and phenyl (which may be substituted by up to three substituents independently selected from the group consisting of nitro, halogen, CF_3, thiomethyl, thioethyl, C_{1-4}-alkyl, and C_{1-4}-alkoxy),

Another subclass of compounds of this invention includes for example compounds of formula I wherein t, u, v, and w are zero and K is not an hydroxy, benzoxy, phenoxy or alkoxy moiety.

Another subclass of compounds of this invention includes for example compounds of formula I wherein t, u, and v are zero and K is not an hydroxy or alkoxy moiety.

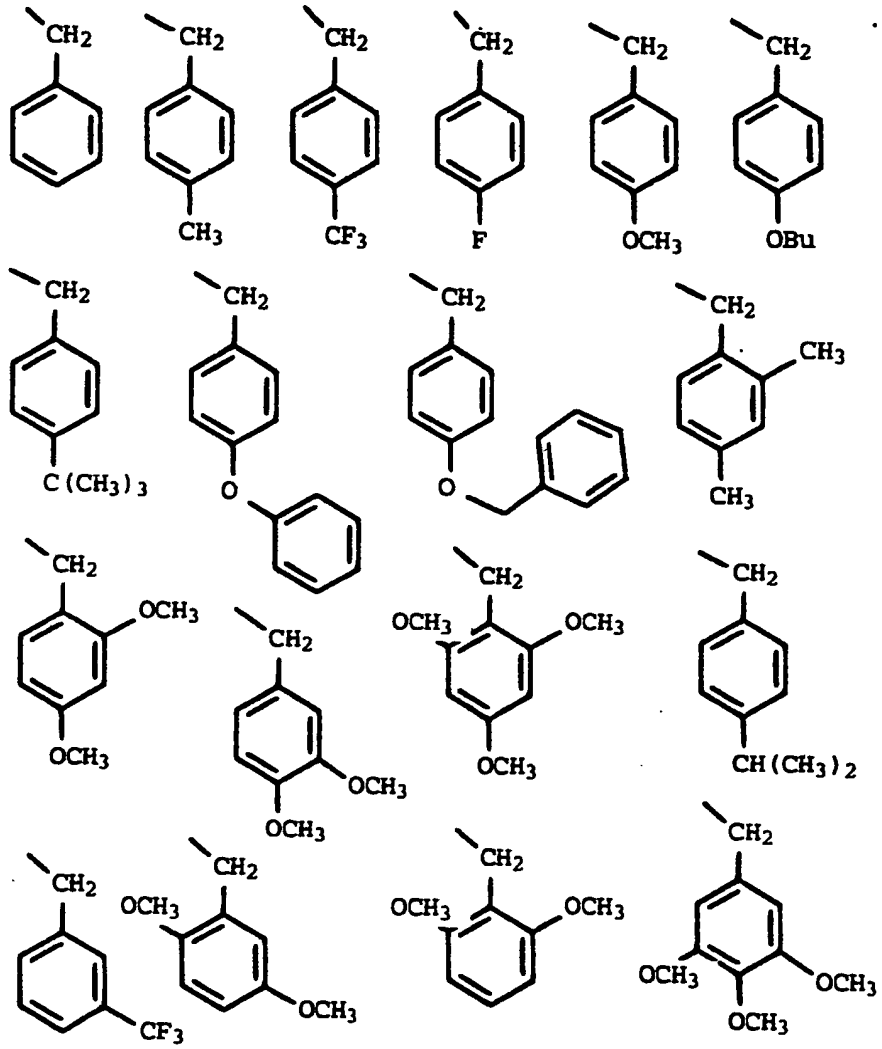
Still another subclass of compounds of this invention includes for example compounds of formula I wherein t, u, v and w are 1 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

Yet another subclass of compounds of this invention includes for example compounds of formula I wherein t, u and v are 1, w is O and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

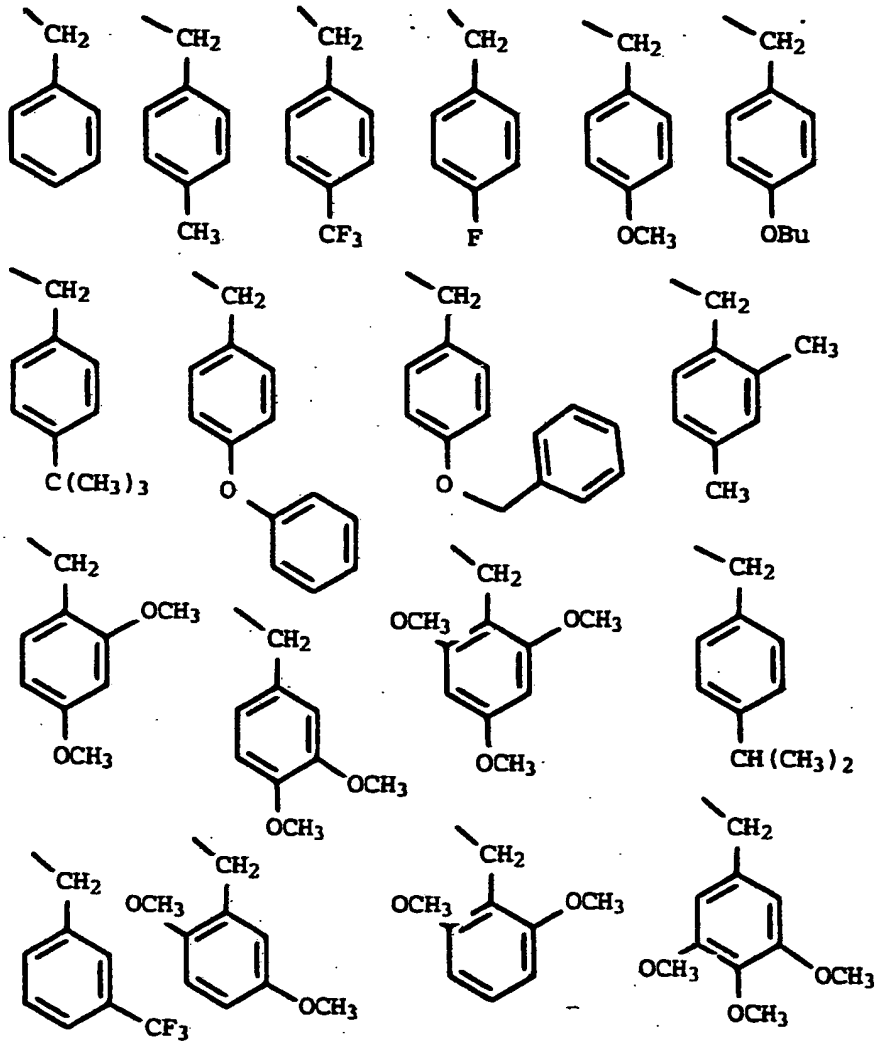
Another subclass of compounds of this invention includes for example compounds of formula I wherein t and u are 1, v and w are 0 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

Preferred are compounds of formula I where the substituents have the following meanings:

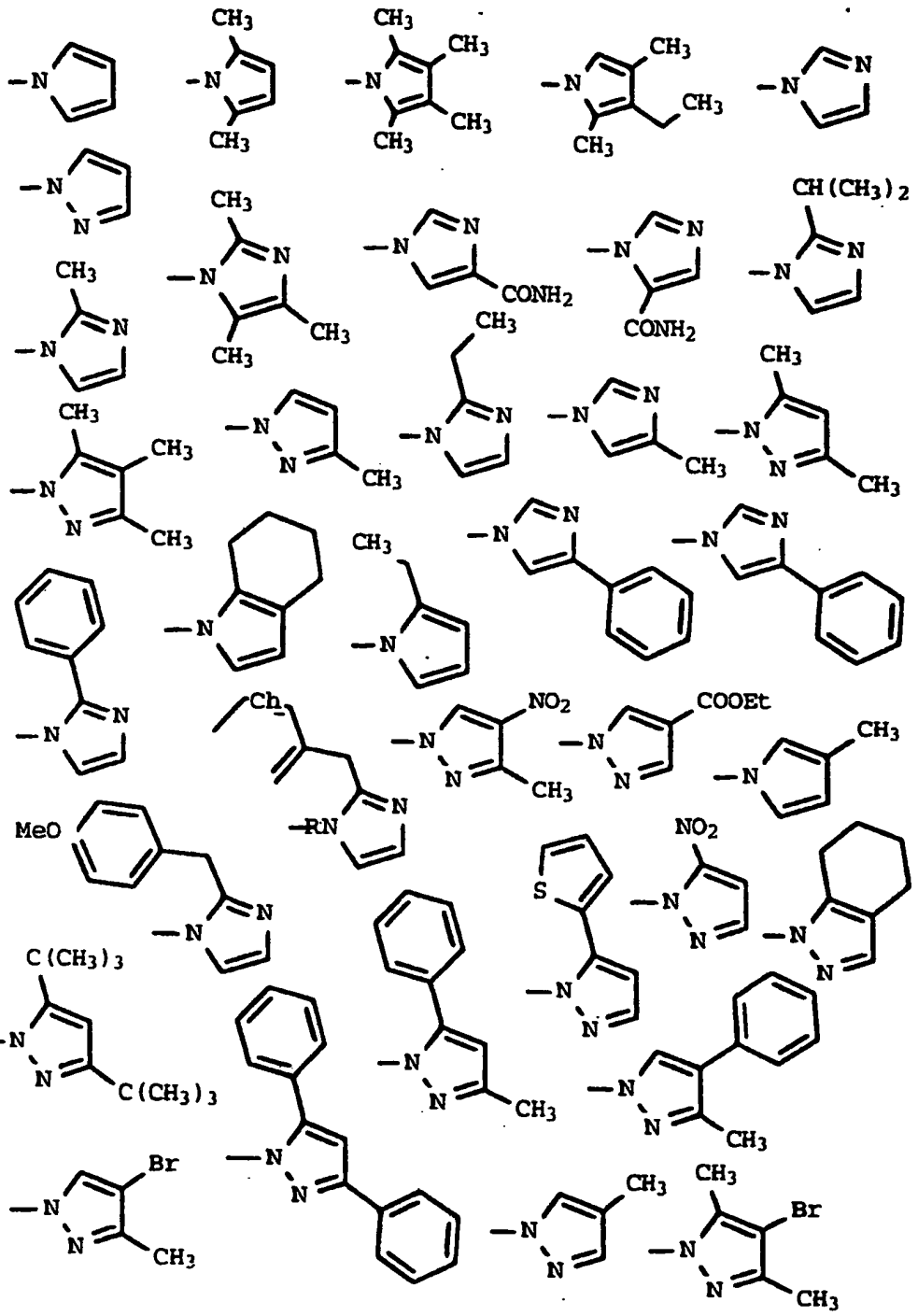
R^1 is ethyl, methyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-fluoroisopropyl, trifluoroisopropyl, isopropyl, propyl, butyl, pentyl, cyclopropyl, cyclopentyl, ureyl, mesyl, tosyl, naphtylsulfonyl, phenylsulfonyl, 2,4,6-trimethylsulfonyl, benzyloxycarbonyl, tert.butyloxycarbonyl, methyloxycarbonyl, morpholinosulfonyl, tert.butylaminosulfonyl, methylaminosulfonyl, lactyl, trifluoroacetyl, NH_2, $N(CH_3)_2$, $N(CH_2CH_3)_2$, $N[CH(CH_3)_2]_2$, amidino, CH_3O-, or one of the residues

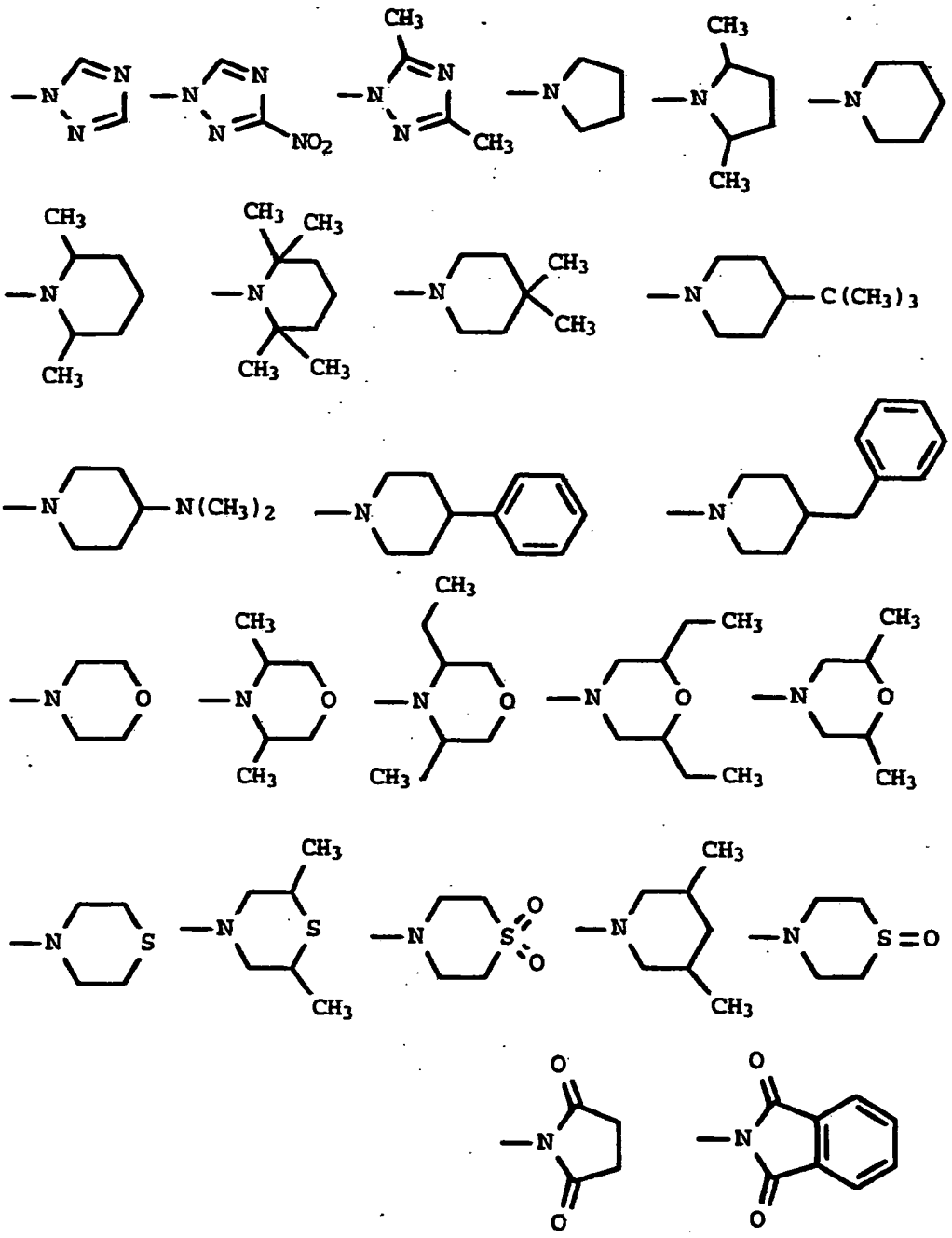


R^2 is hydrogen, methyl, ethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-fluoroisopropyl, trifluoroisopropyl, isopropyl, propyl, butyl, cyclopropyl, formyl, acetyl, propionyl, $(CH_3)_2CHCO-$, pivaloyl, benzoyl or one of the residues



or R^1–N–R^2 together is one of the following residues:

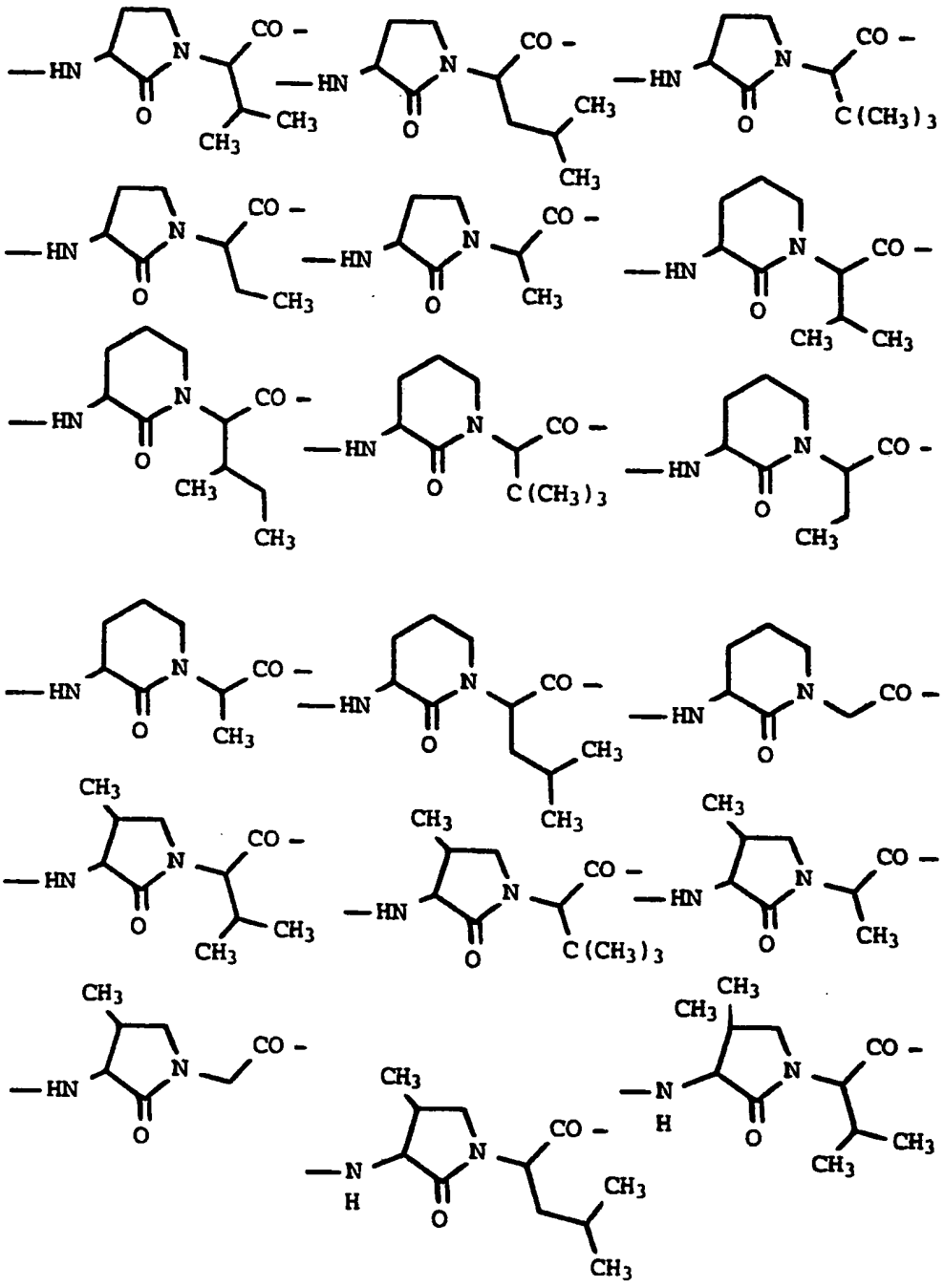


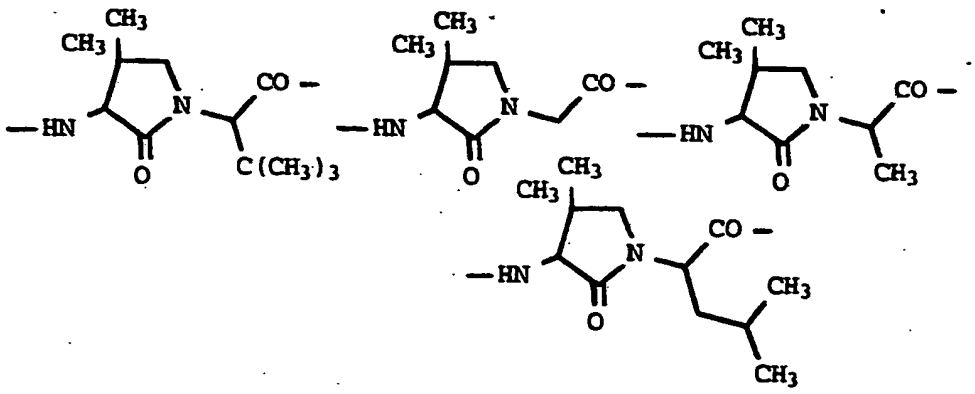


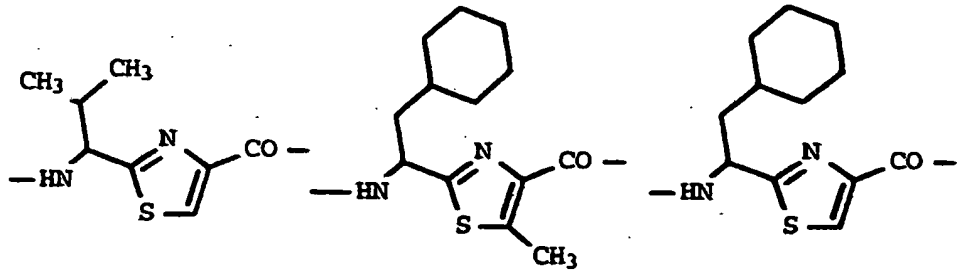
A, B, D, E, F, G and X have the meanings as described above;

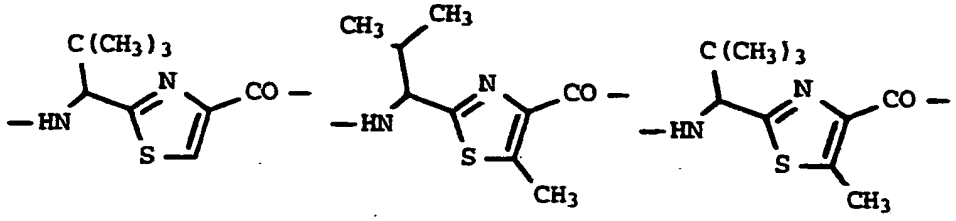
t, u, v and w are independently 0 or 1;

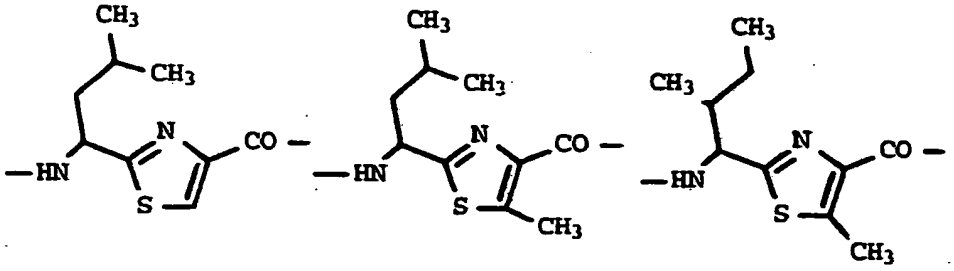
A and B together are

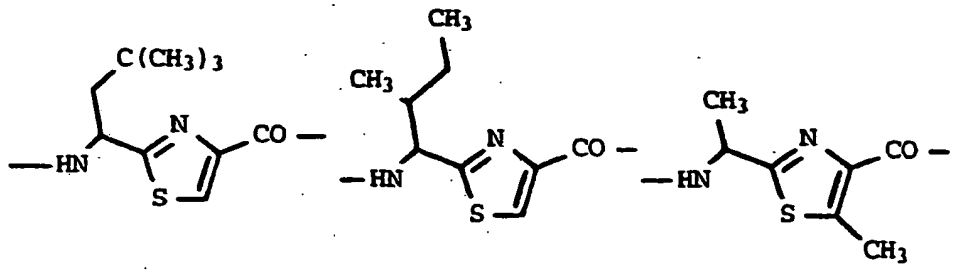


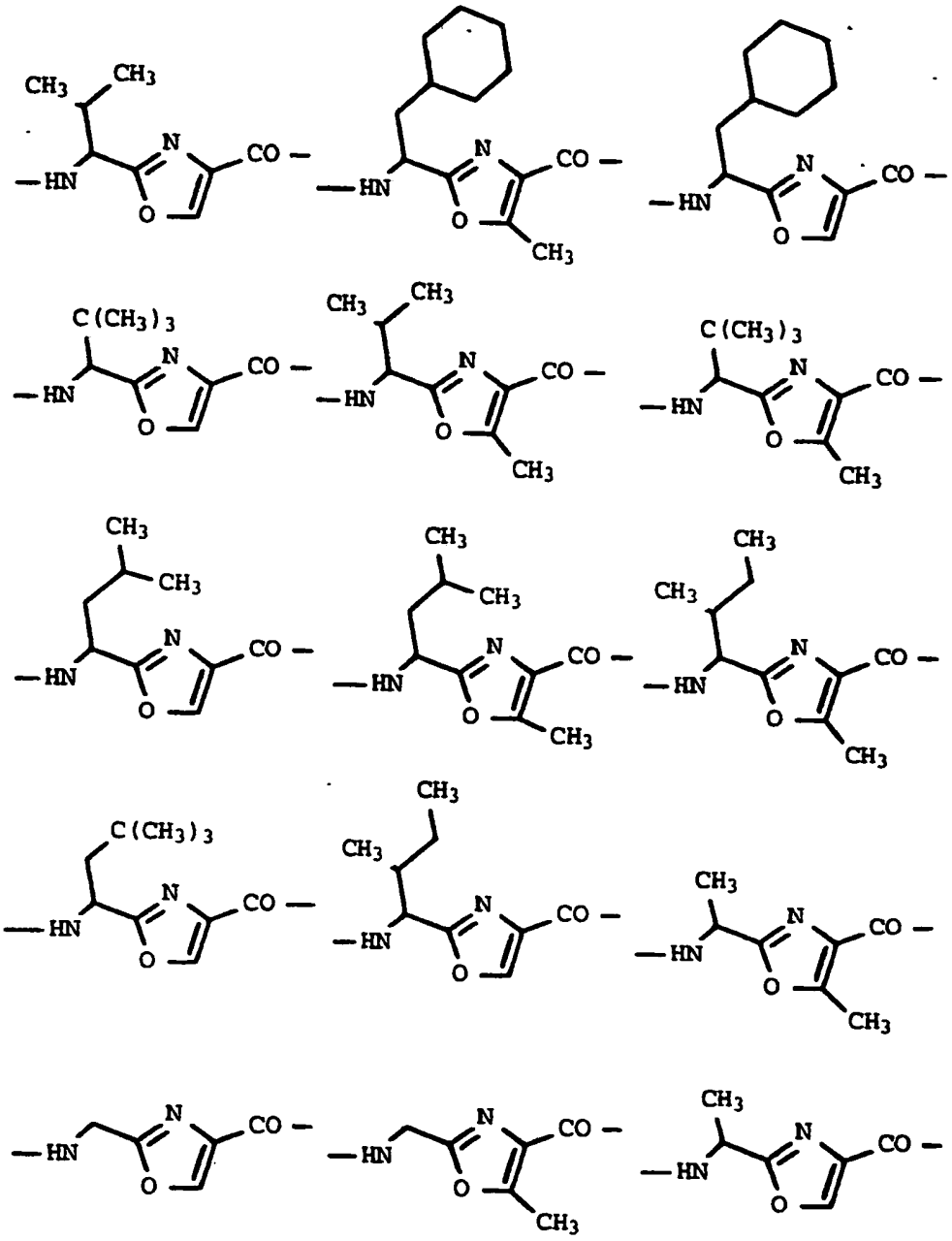


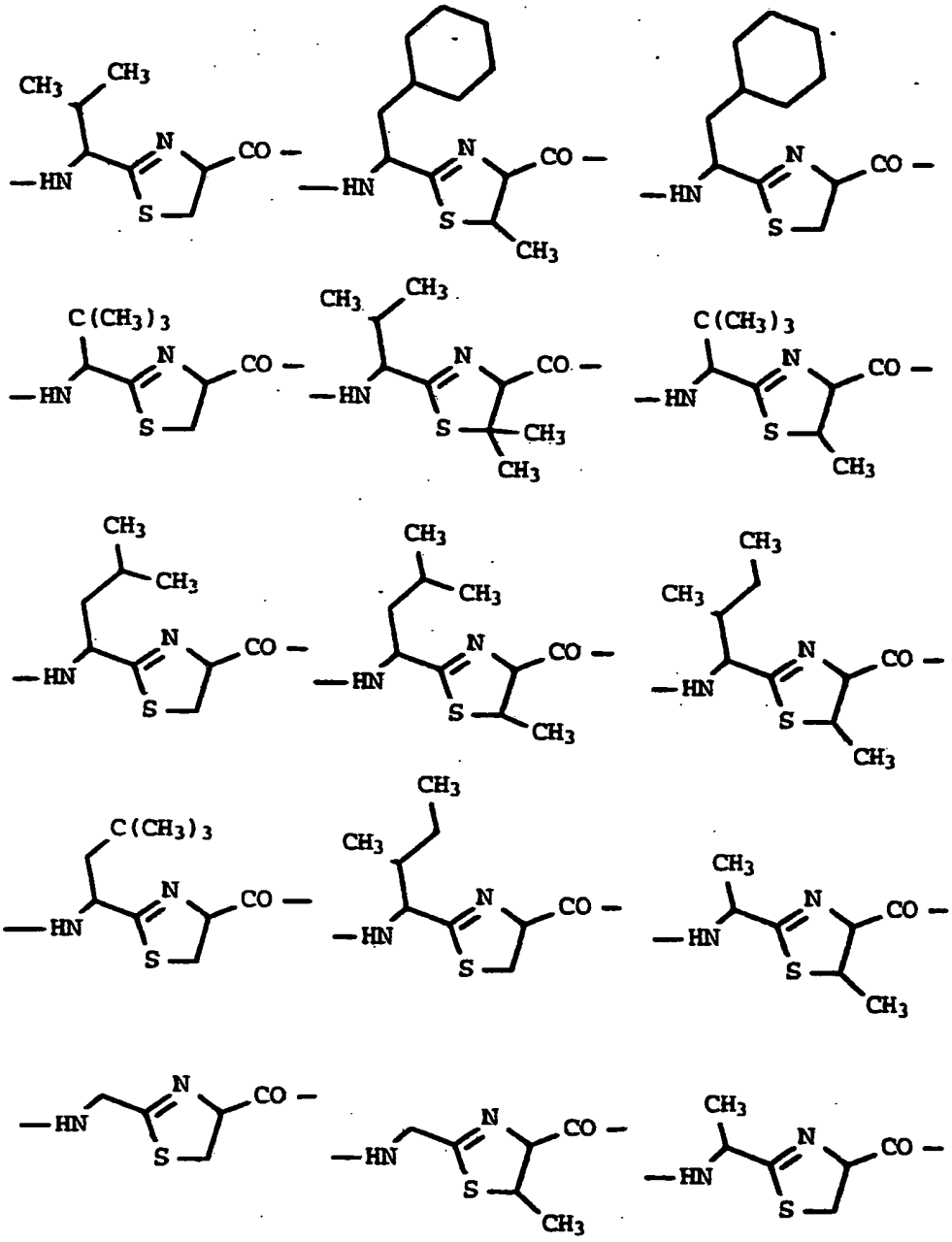


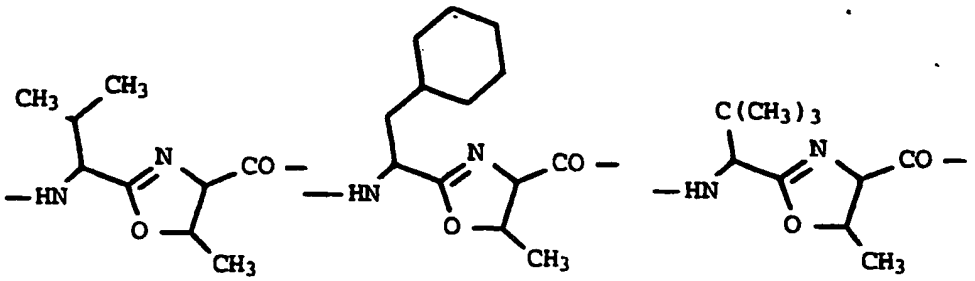


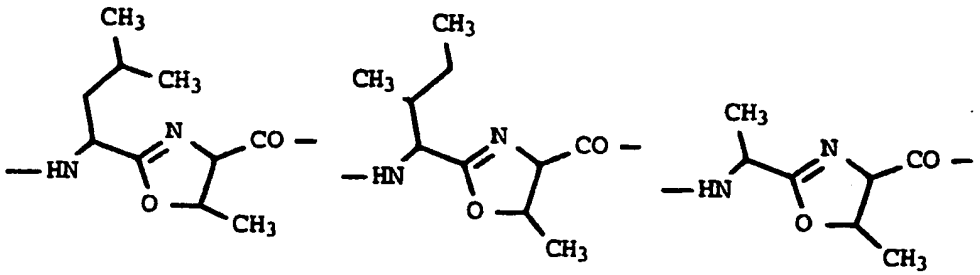


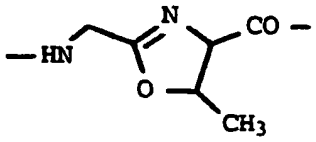




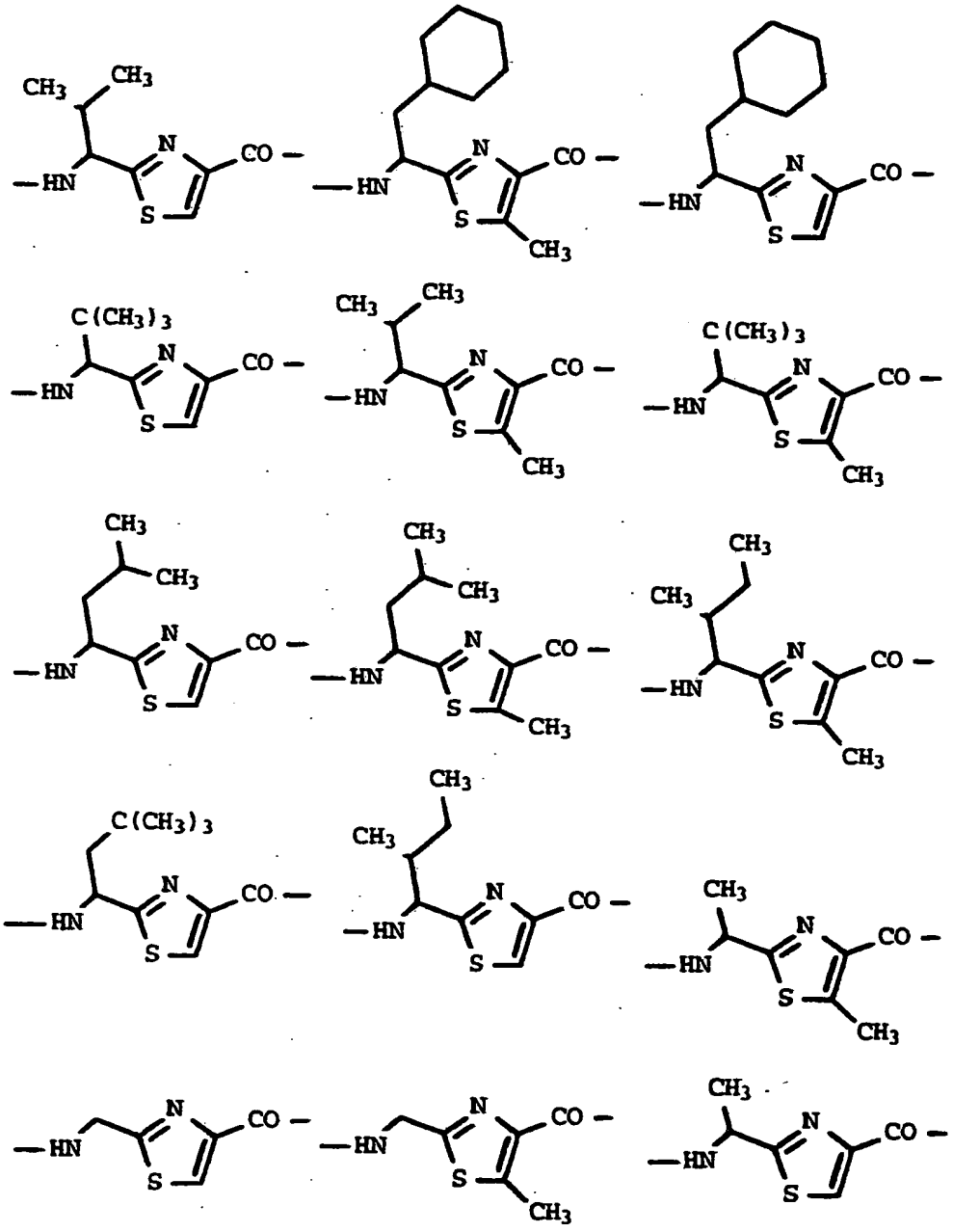


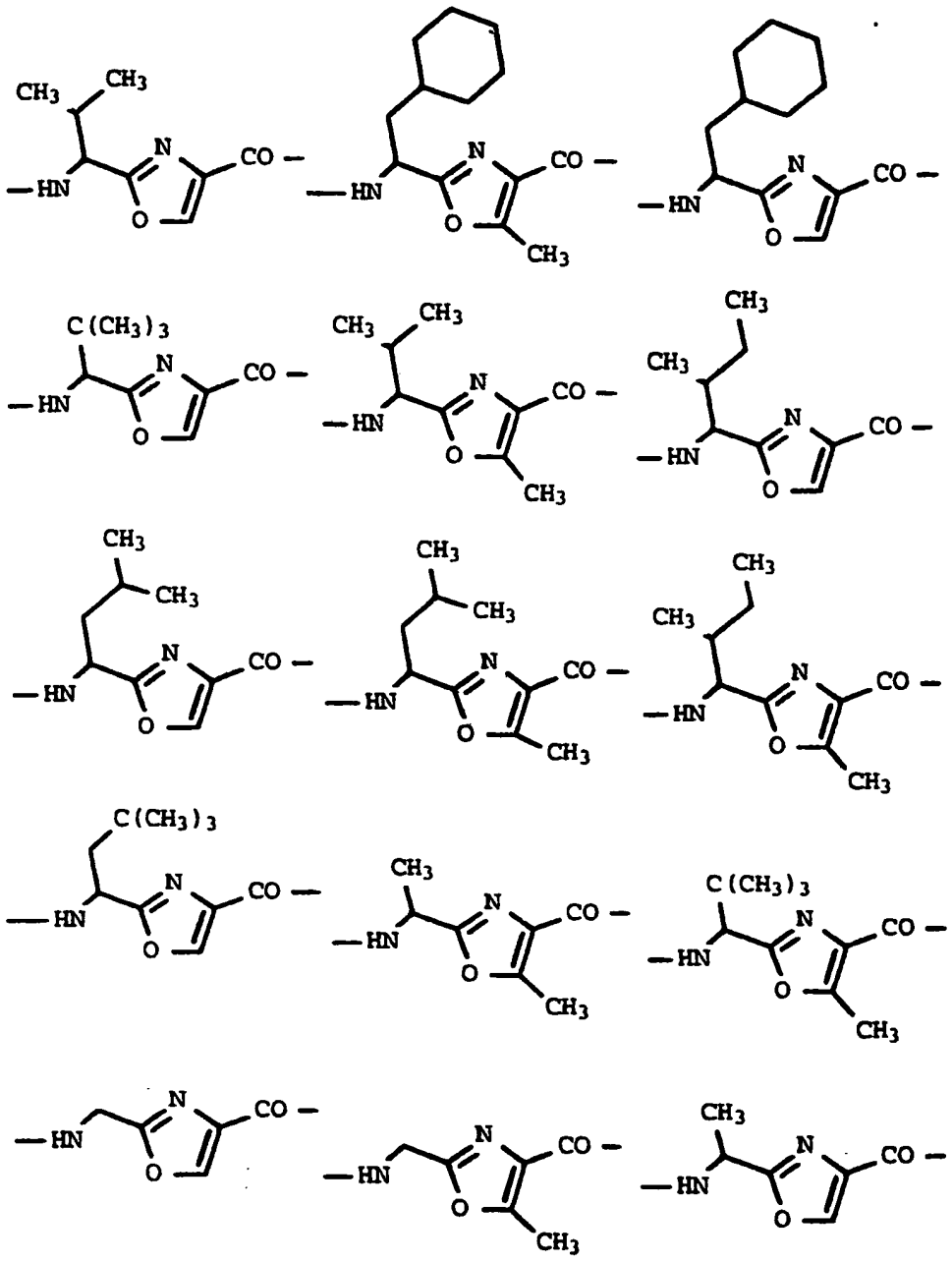


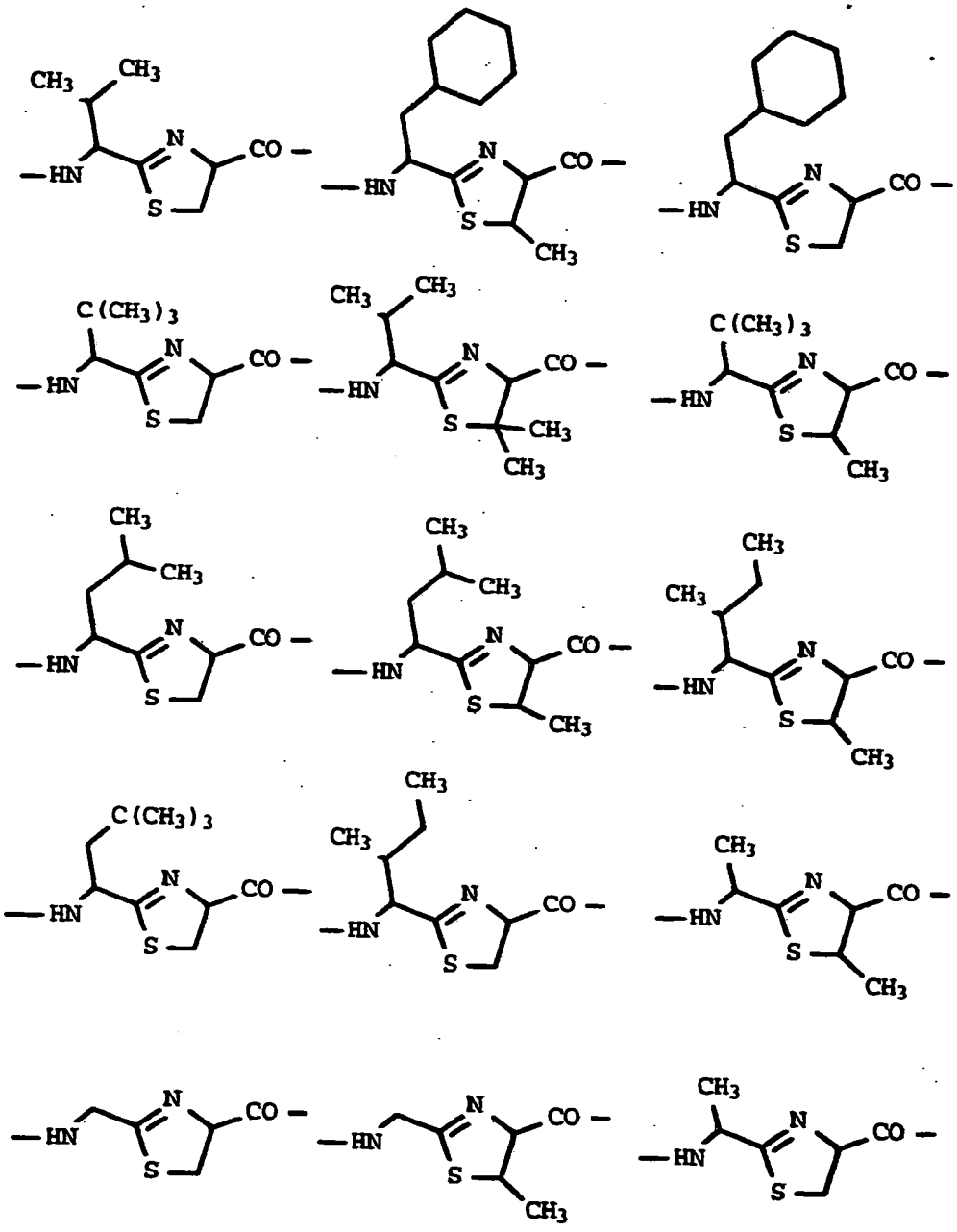


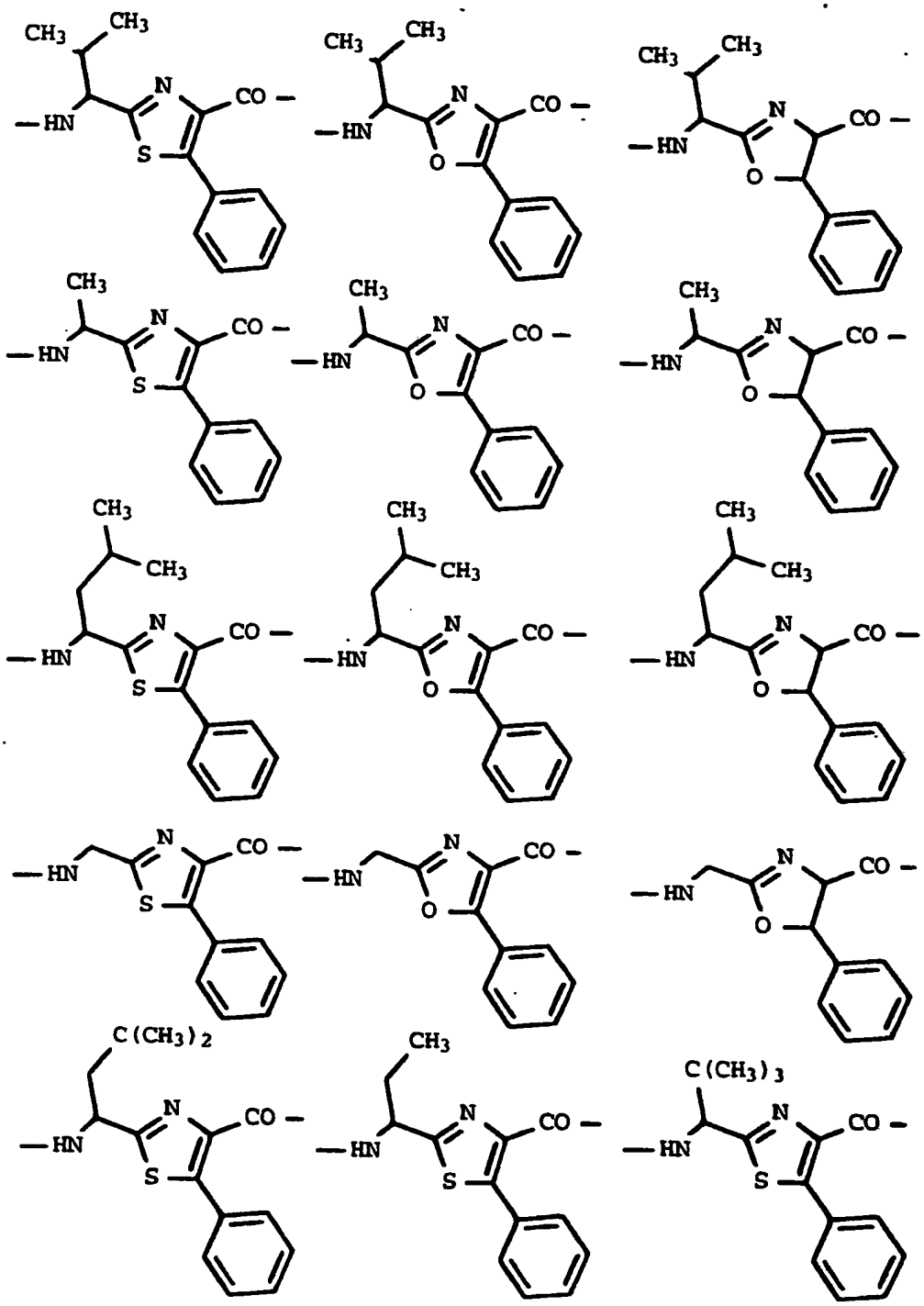


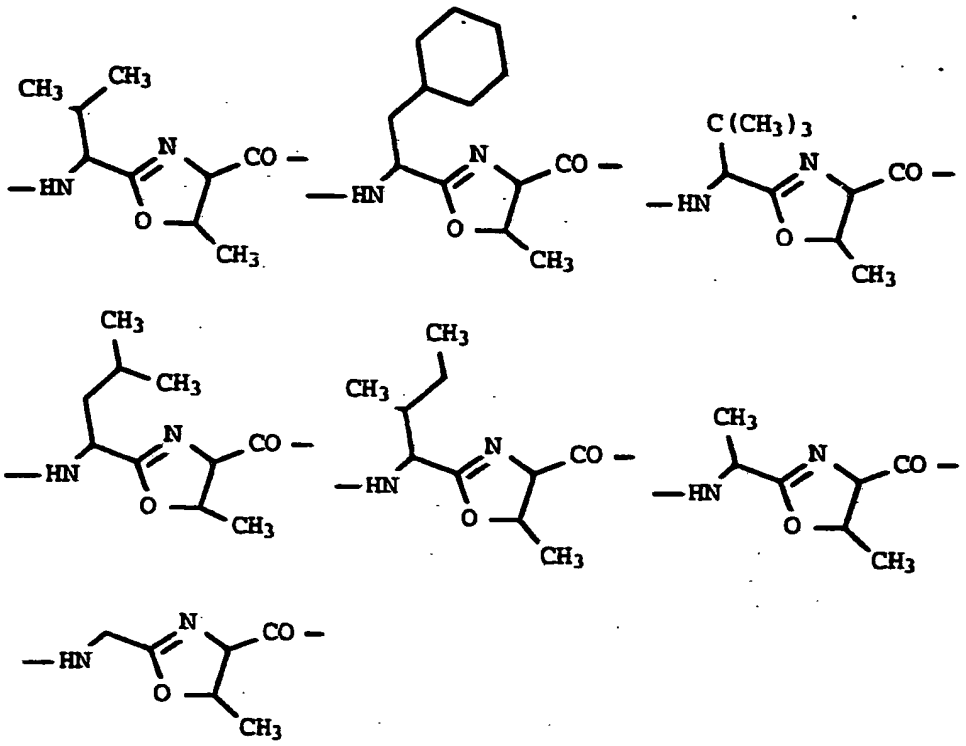
F and G together are



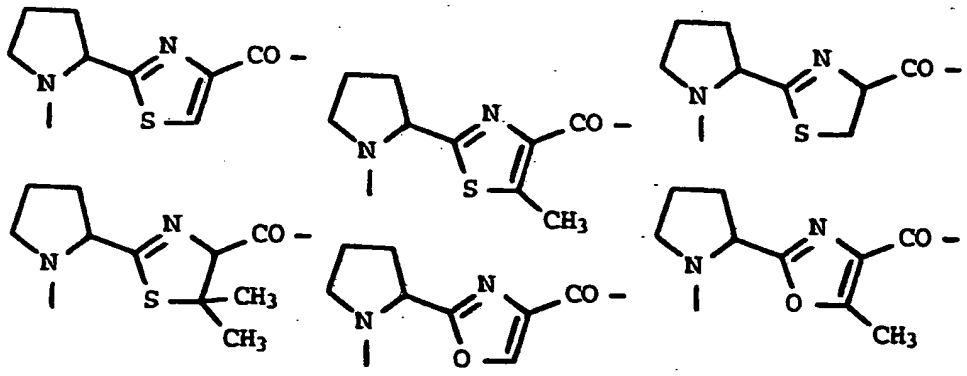


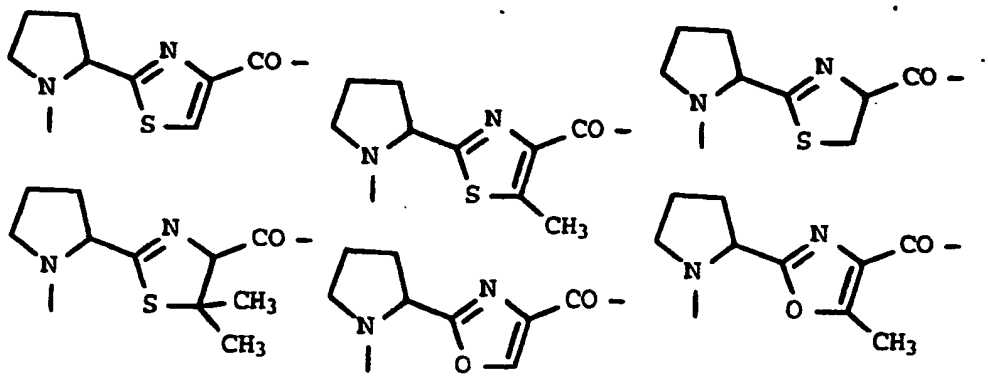




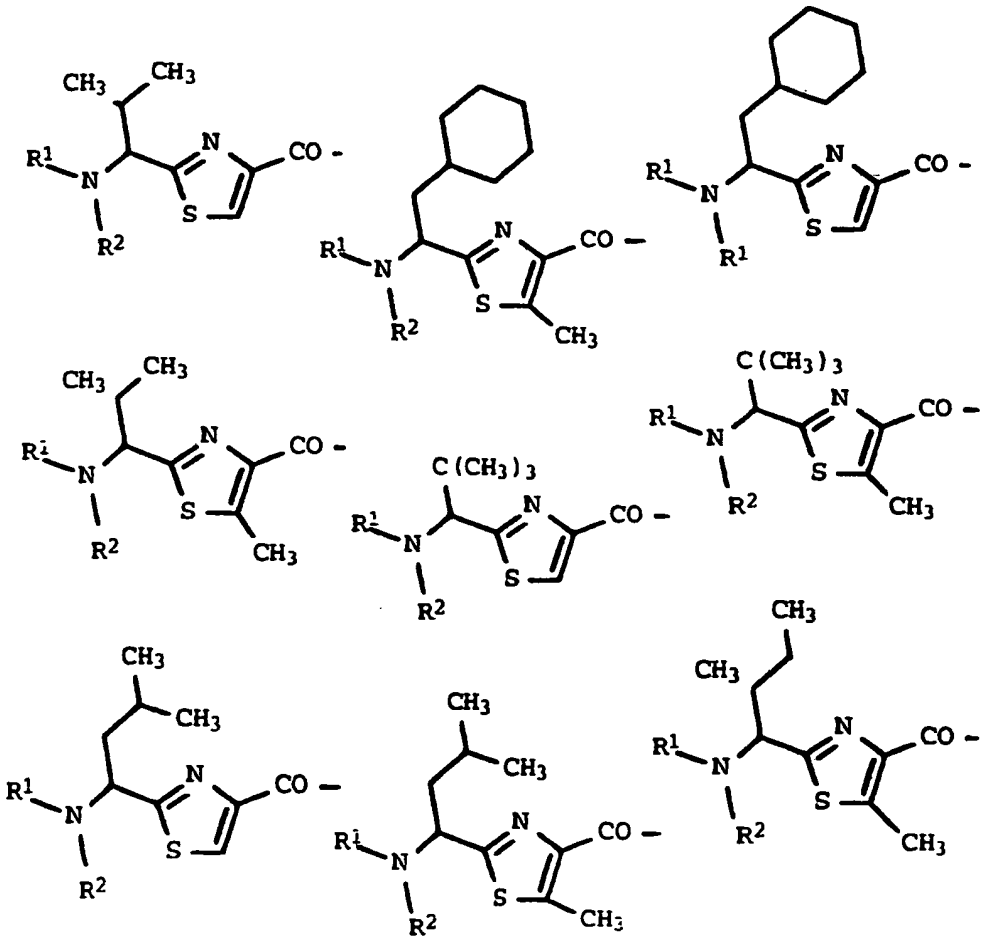


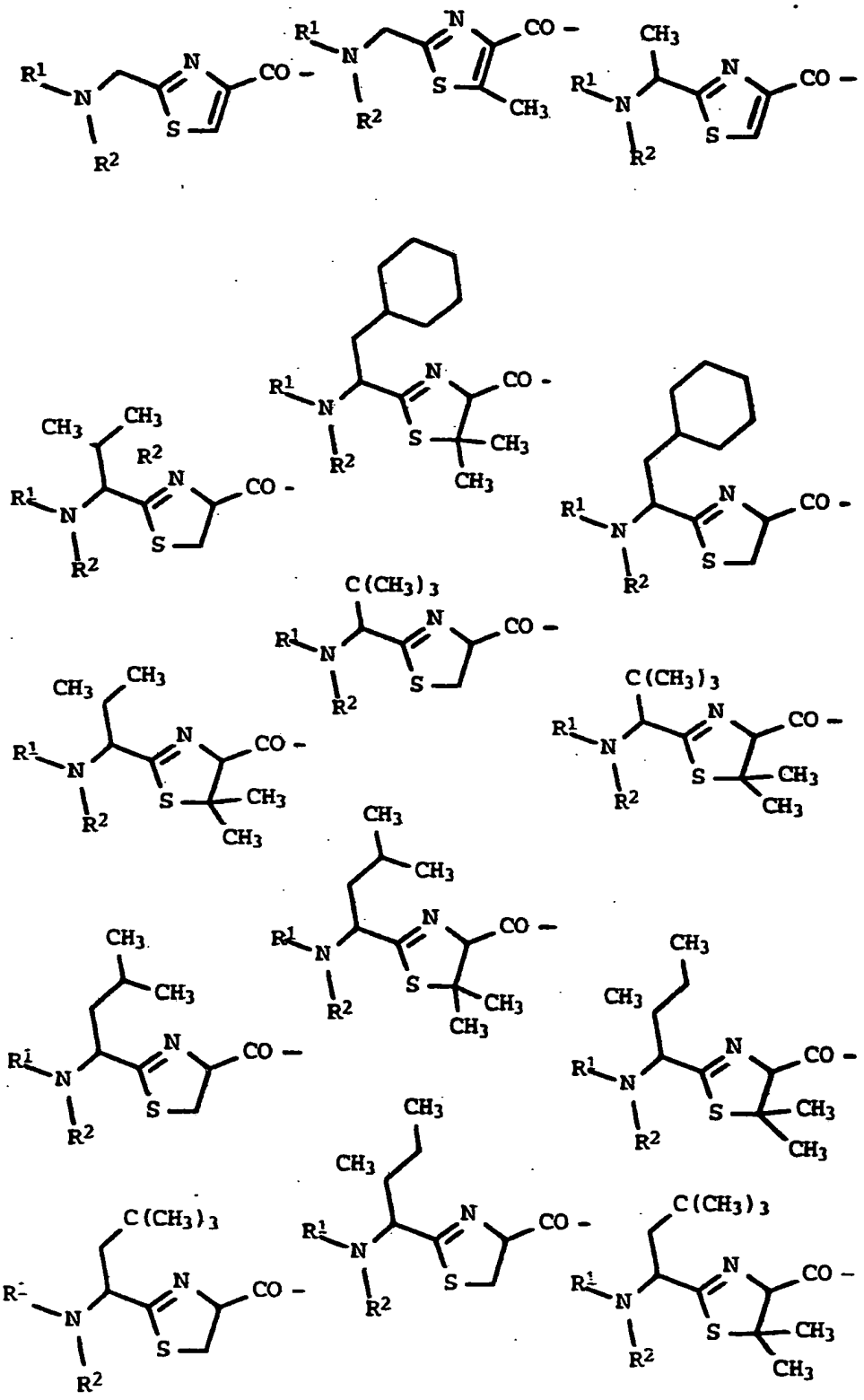
E and F together are

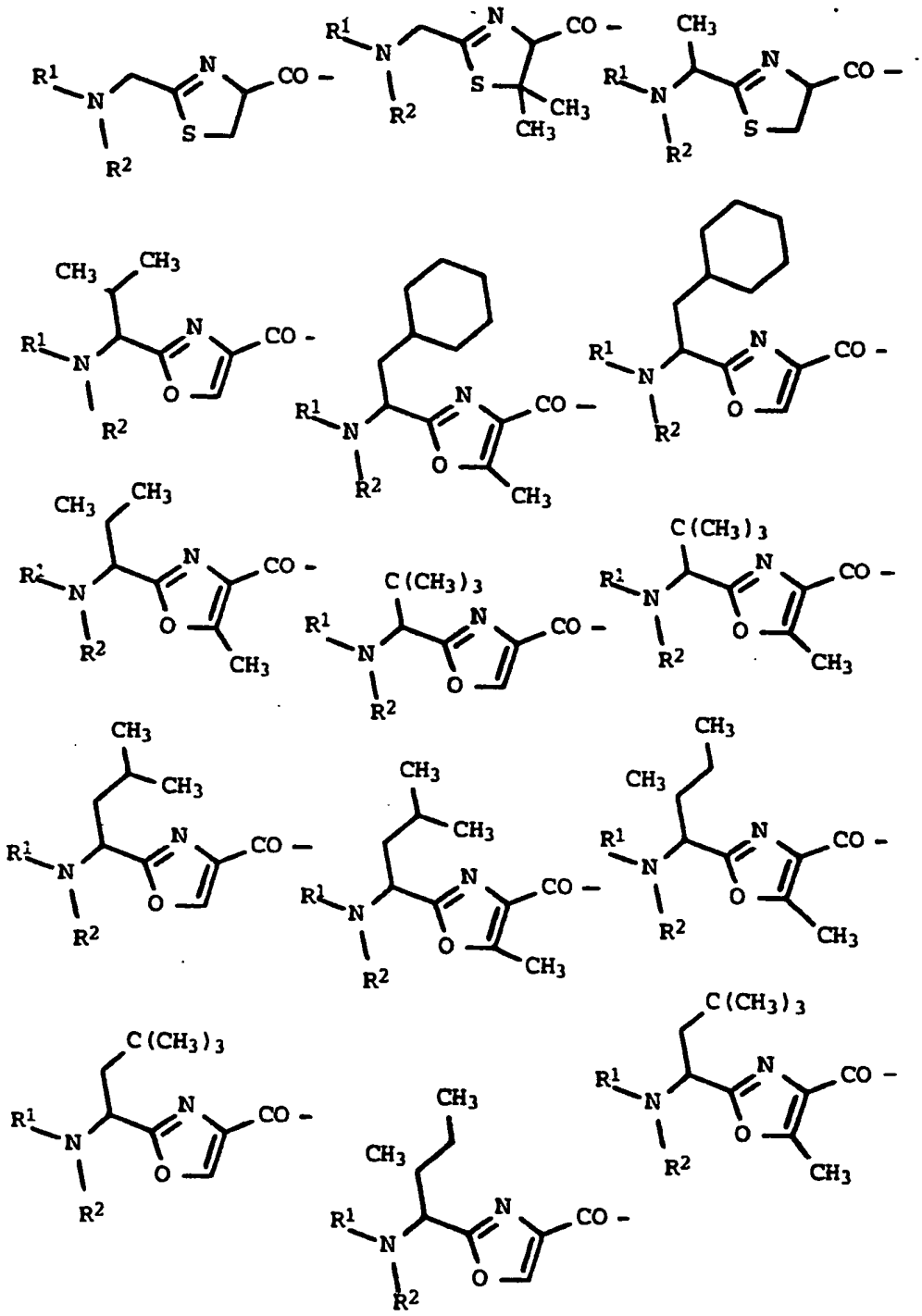


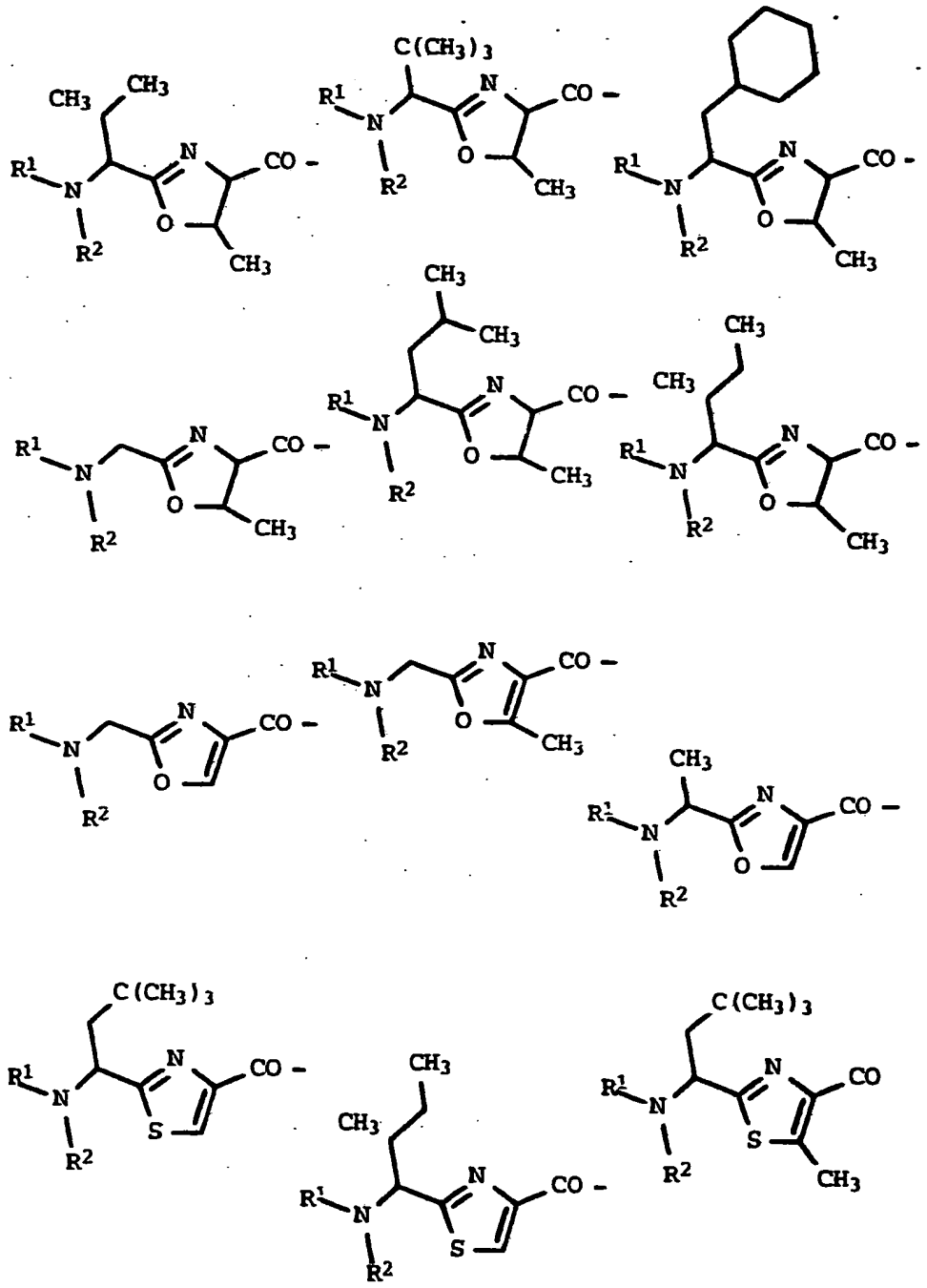


R^1R^2N-CHX-CO and A together are

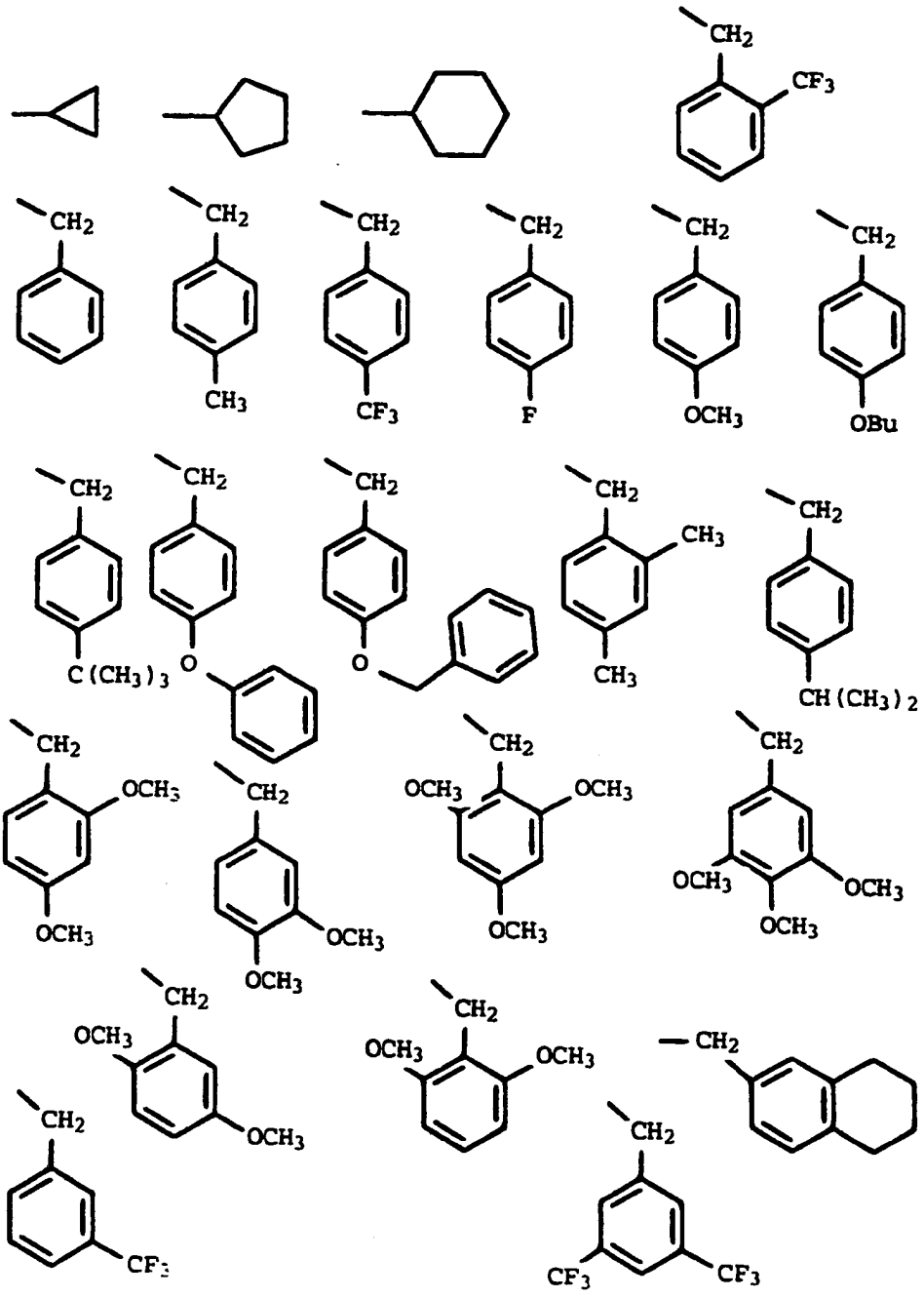




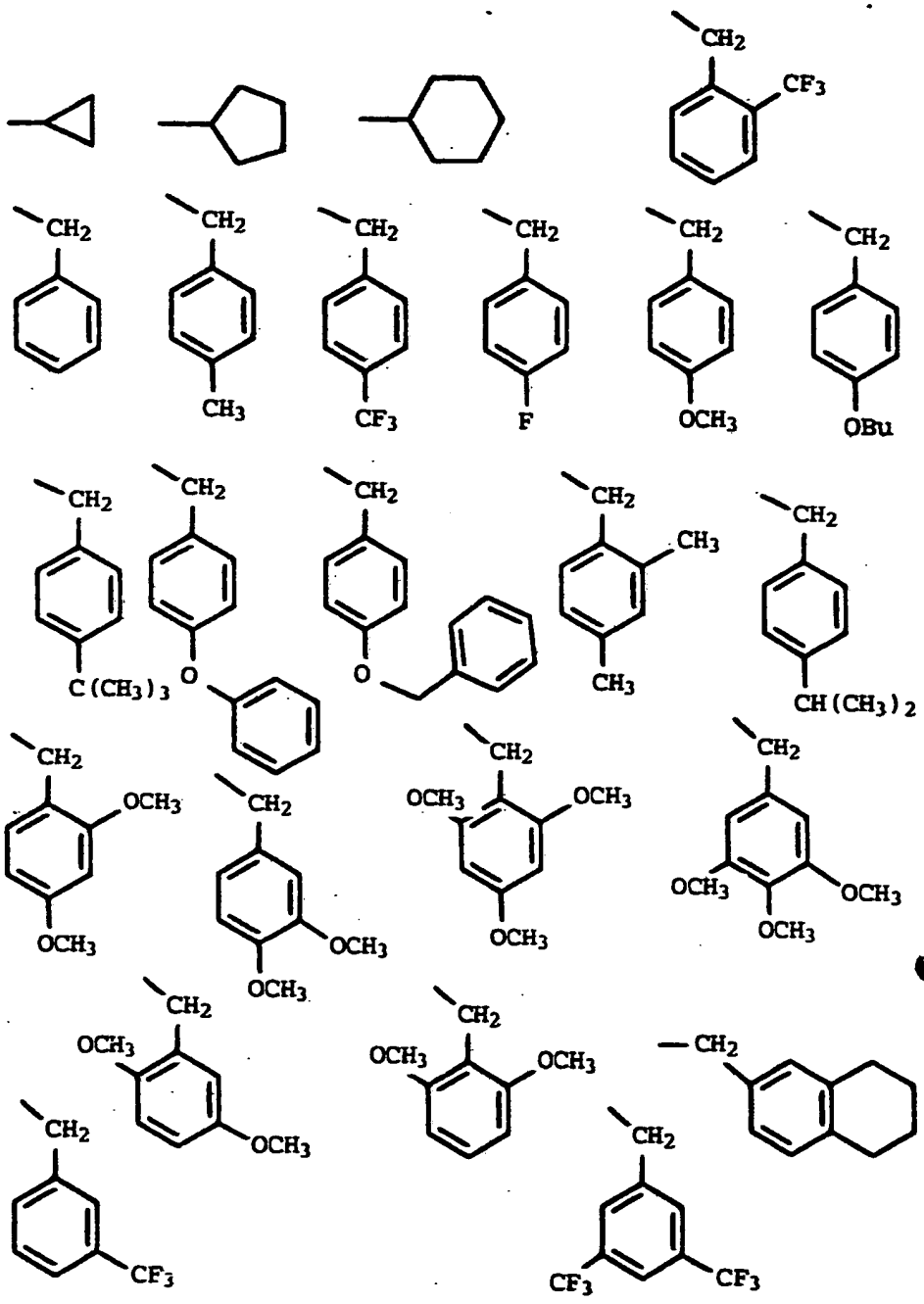


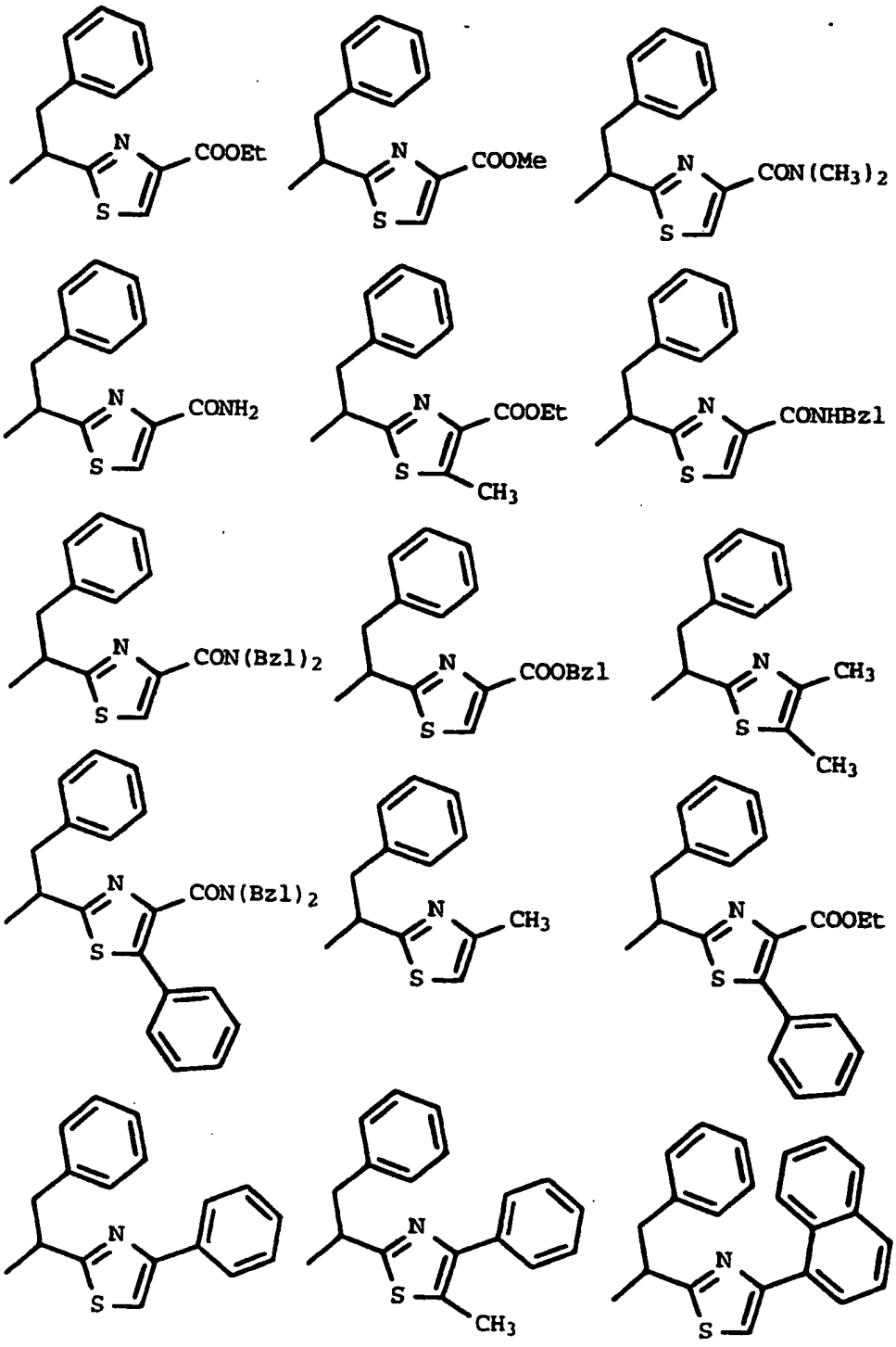


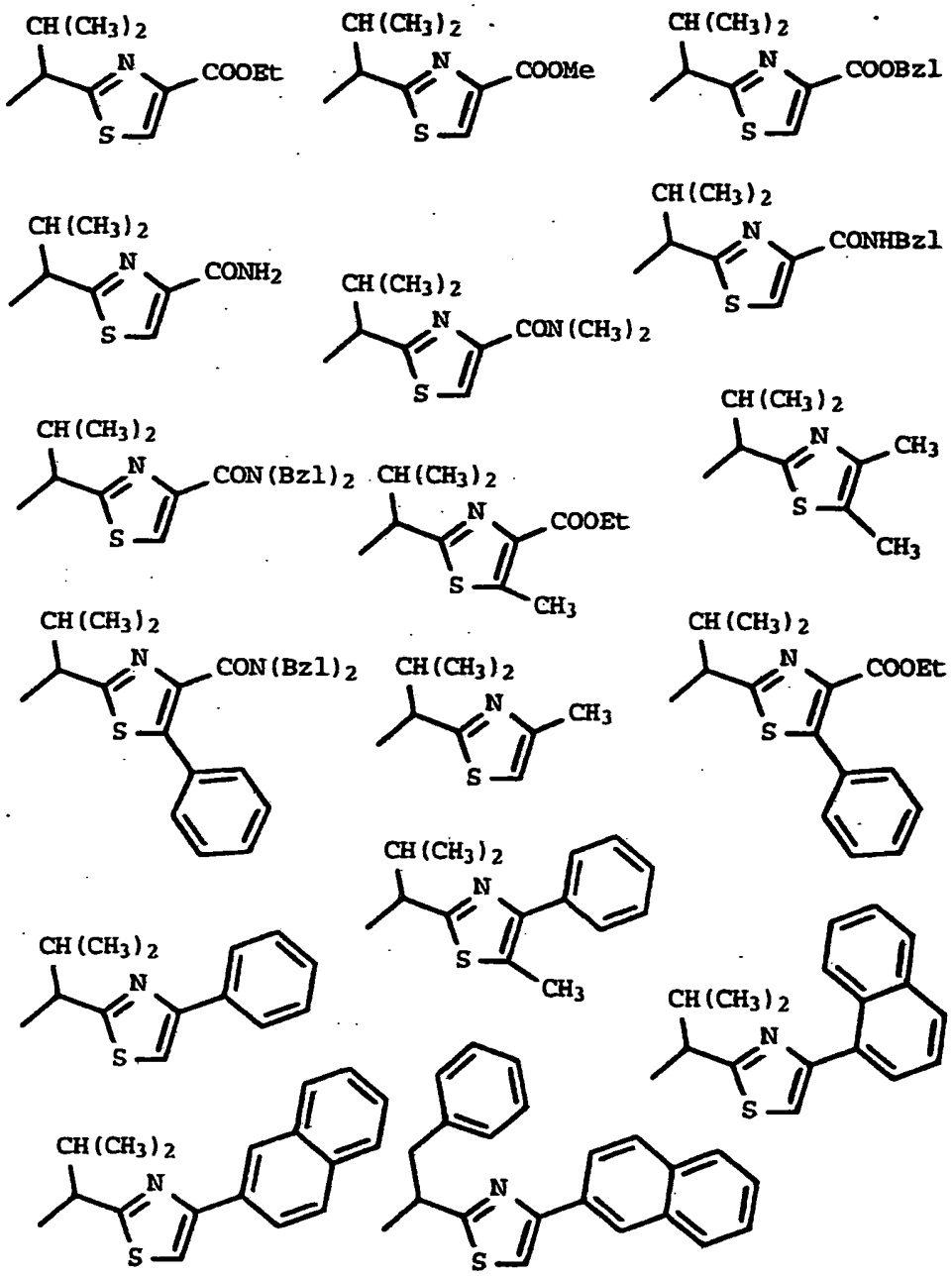
R^5 is hydrogen, methyl, ethyl, 2-fluoroethyl, 2,2-difluoroethyl, trifluoroisopropyl, propyl, soproypyl, or

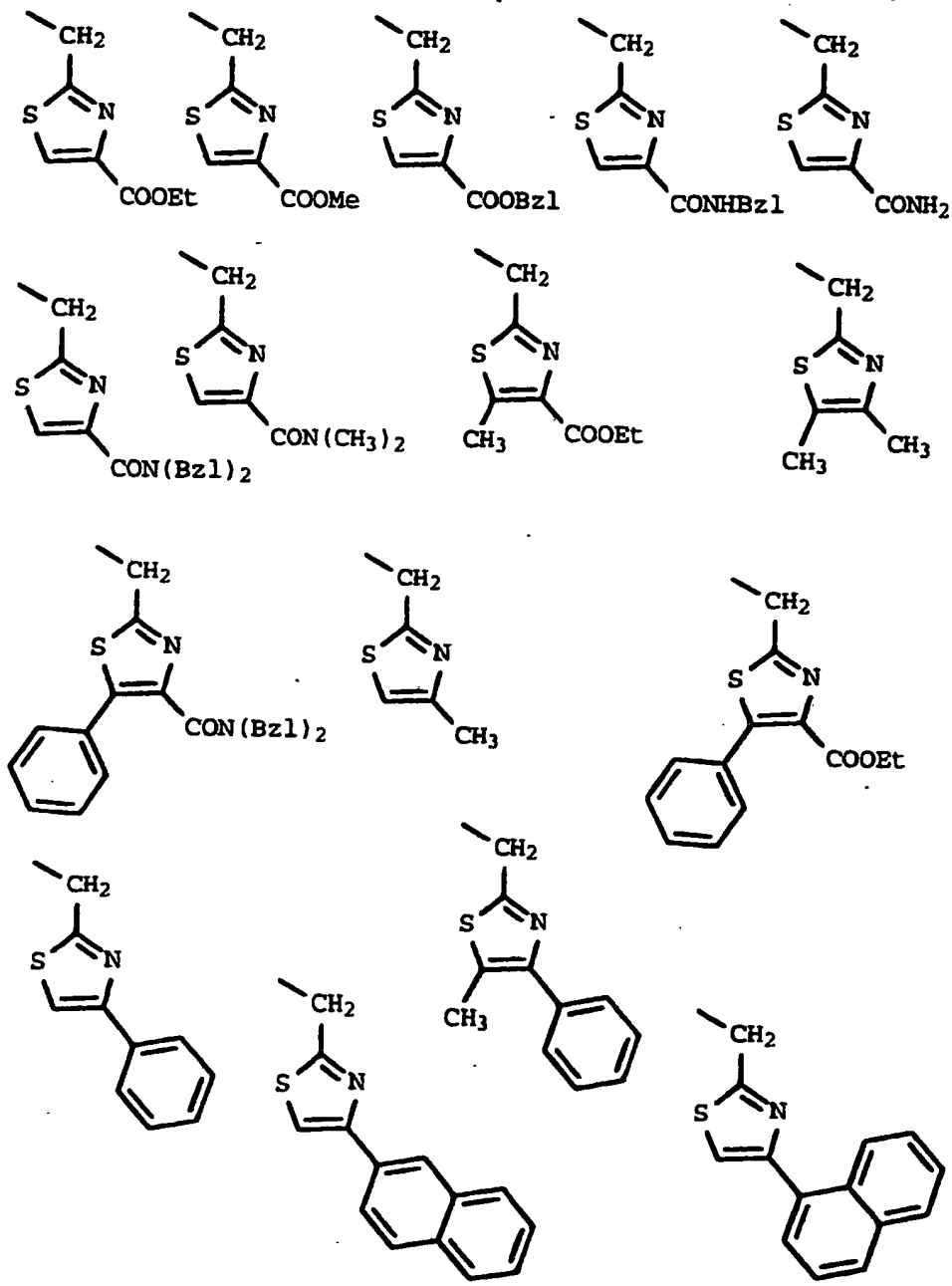


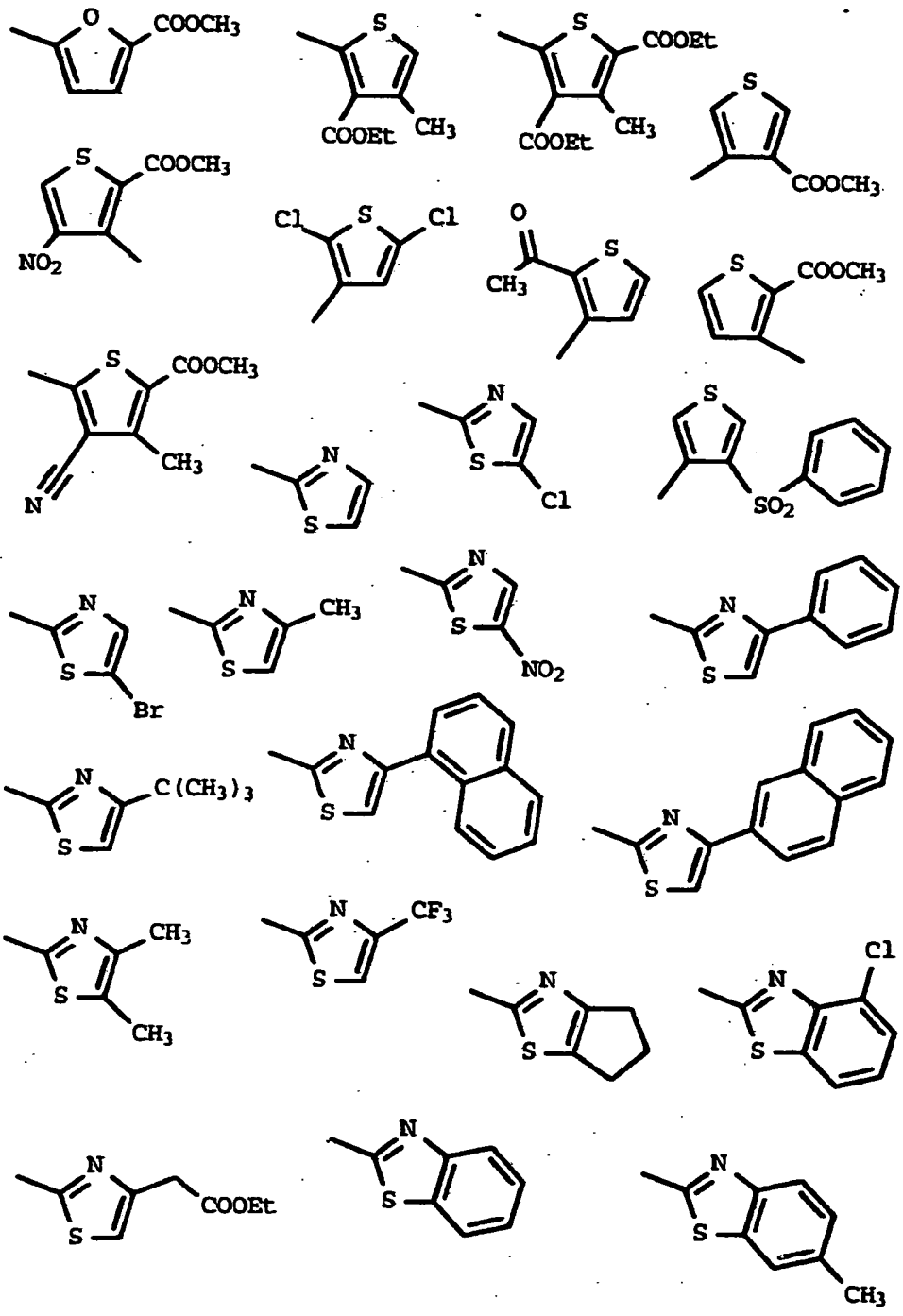
R^6 is hydrogen, methyl, ethyl, 2-fluoroethyl, 2,2-difluoroethyl, trifluoroethyl, trifluoroisopropyl, propyl, isopropyl, tert-butyl, or

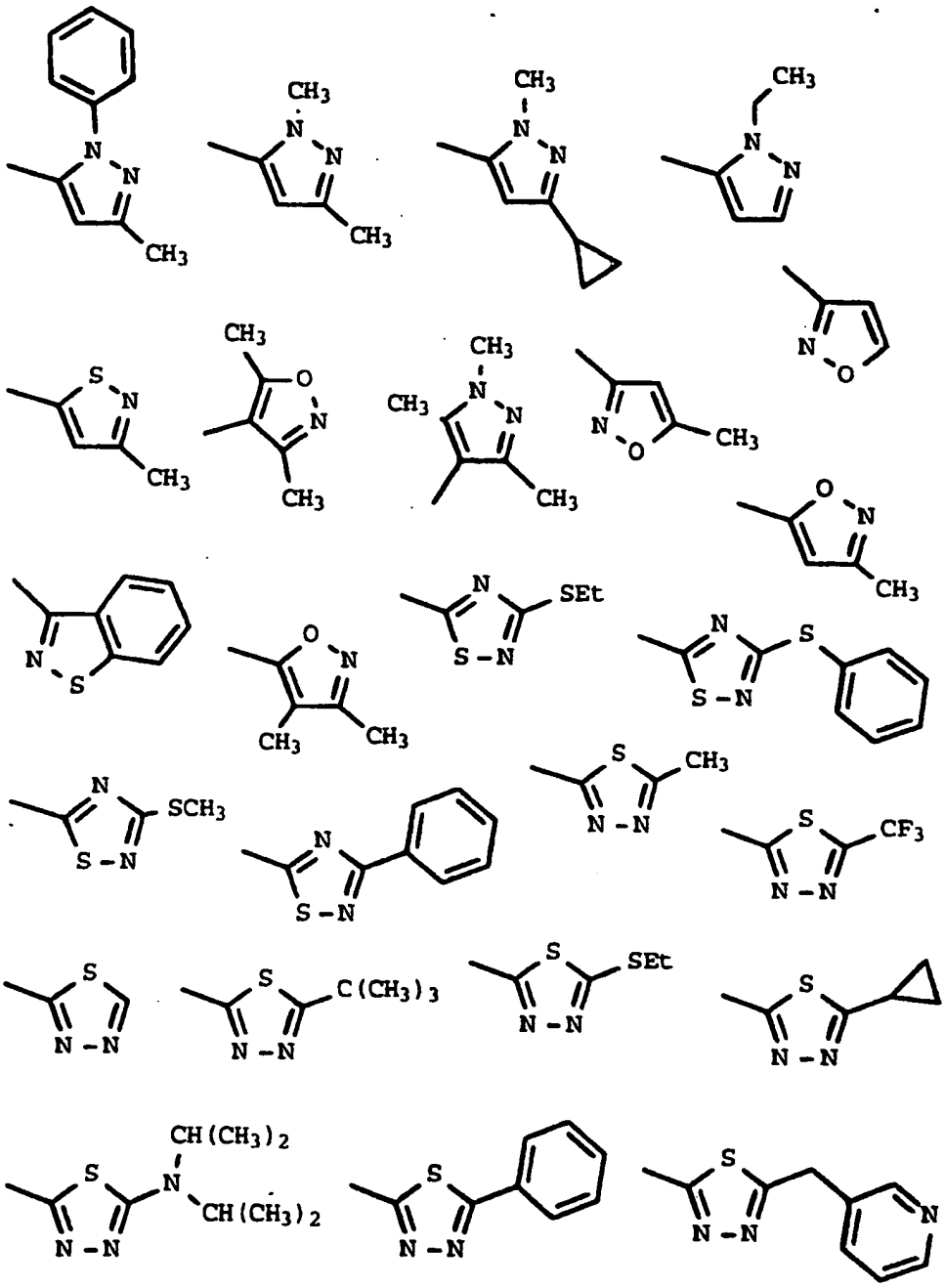


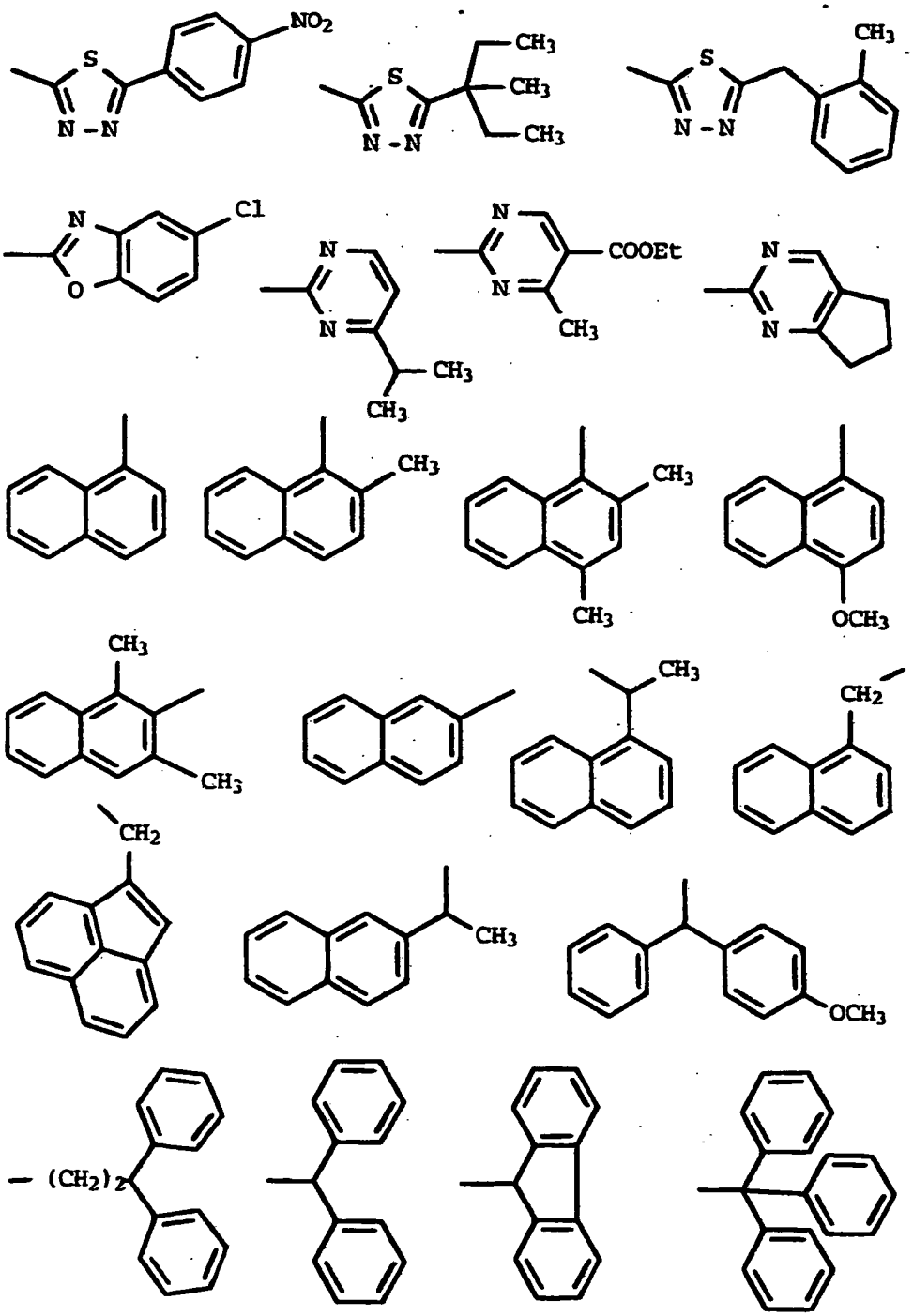

COOEt
COOMe
CON(CH3)2
CONH2
COOEt
CH3
CONHBzl
CON(Bzl)2
COOBzl
CH3
CH3
CON(Bzl)2
CH3
COOEt
CH3

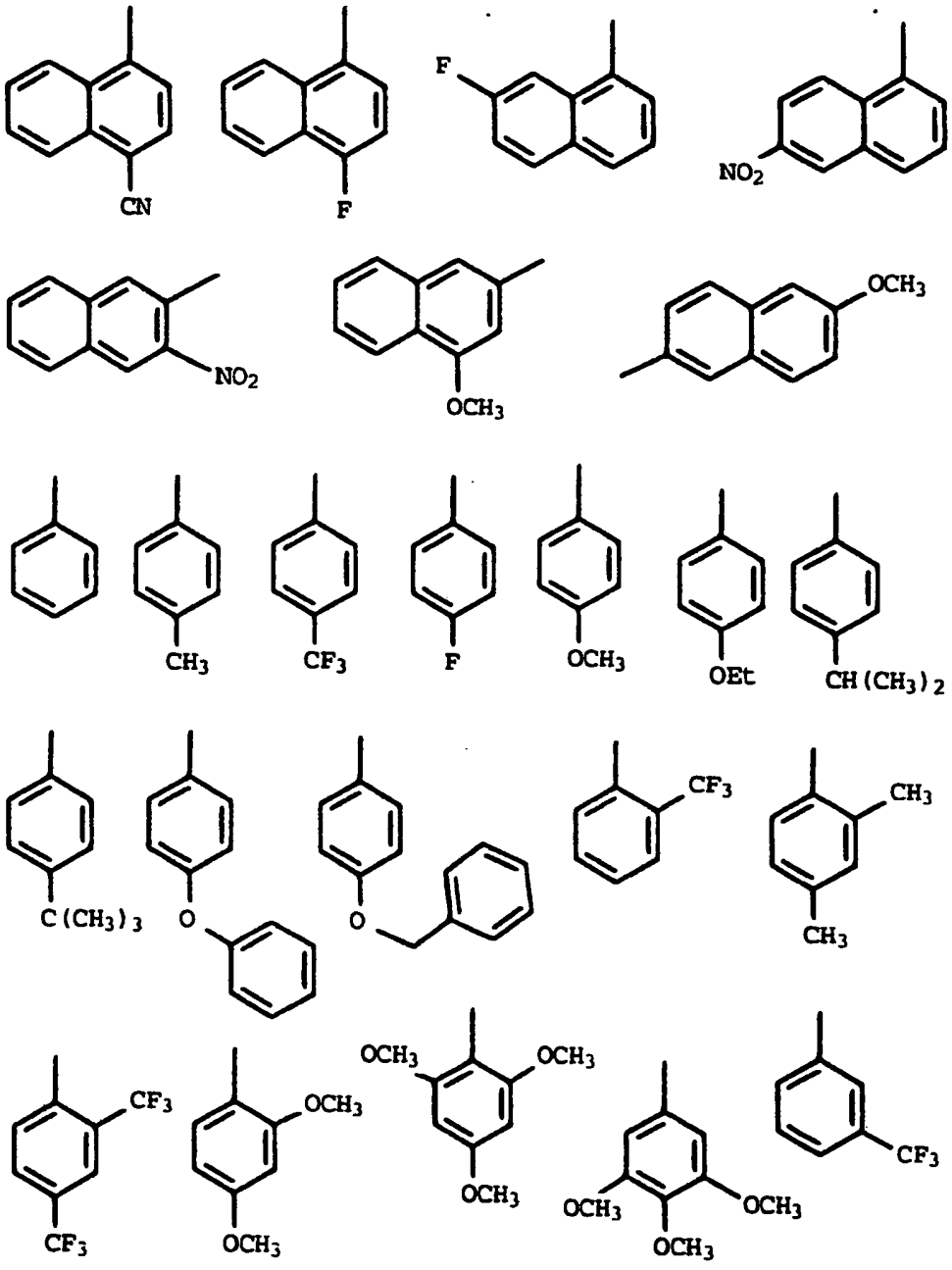

CH(CH3)2
COOEt
CH(CH3)2
COOMe
CH(CH3)2
COOBzl
CH(CH3)2
CONH2
CH(CH3)2
CONHBzl
CH(CH3)2
CON(CH3)2
CH(CH3)2
CON(Bzl)2
CH(CH3)2
COOEt
CH3
CH(CH3)2
CH3
CH(CH3)2
CON(Bzl)2
CH(CH3)2
CH3
CH(CH3)2
COOEt
CH(CH3)2
CH3
CH(CH3)2
CH(CH3)2
CH(CH3)2
N
S

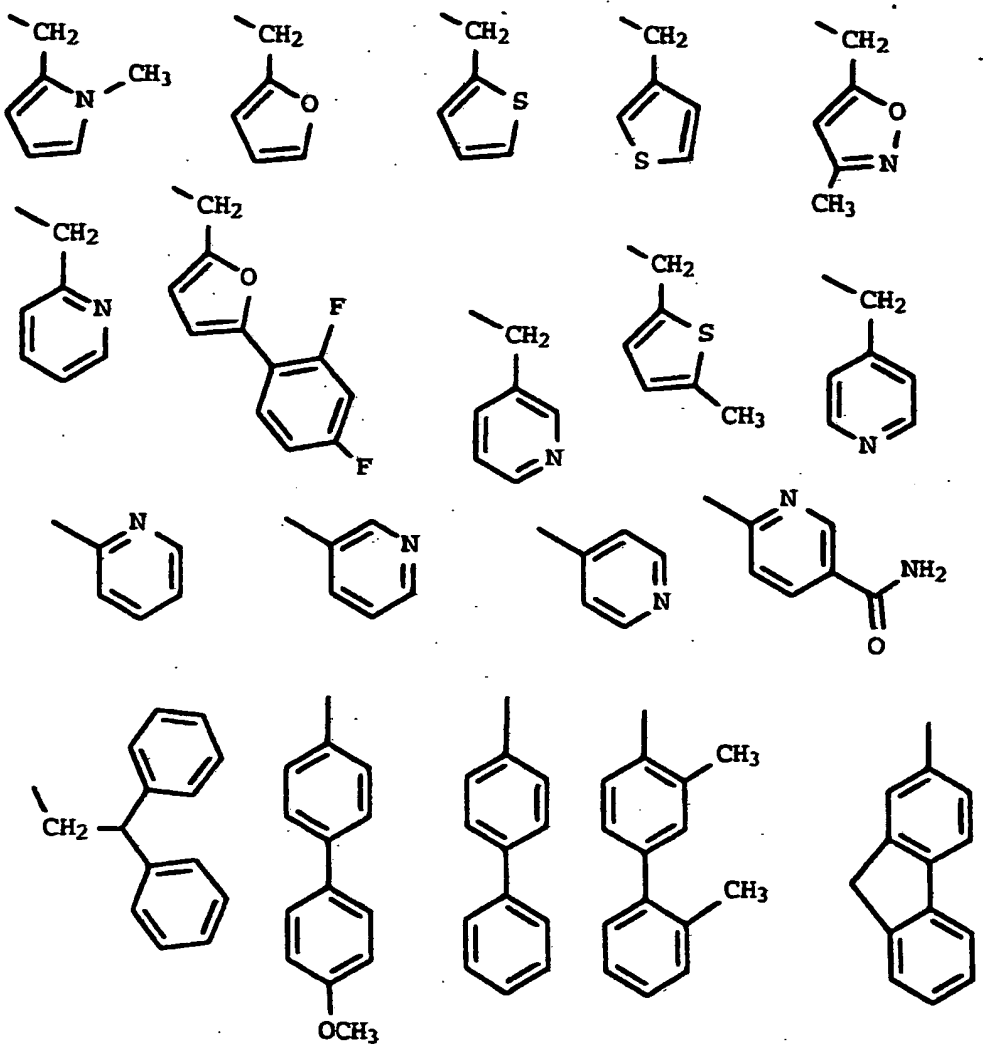

CH2
S
N
COOEt
COOMe
COOBzl
CONHBzl
CONH2
CON(CH3)2
CON(Bzl)2
CH3



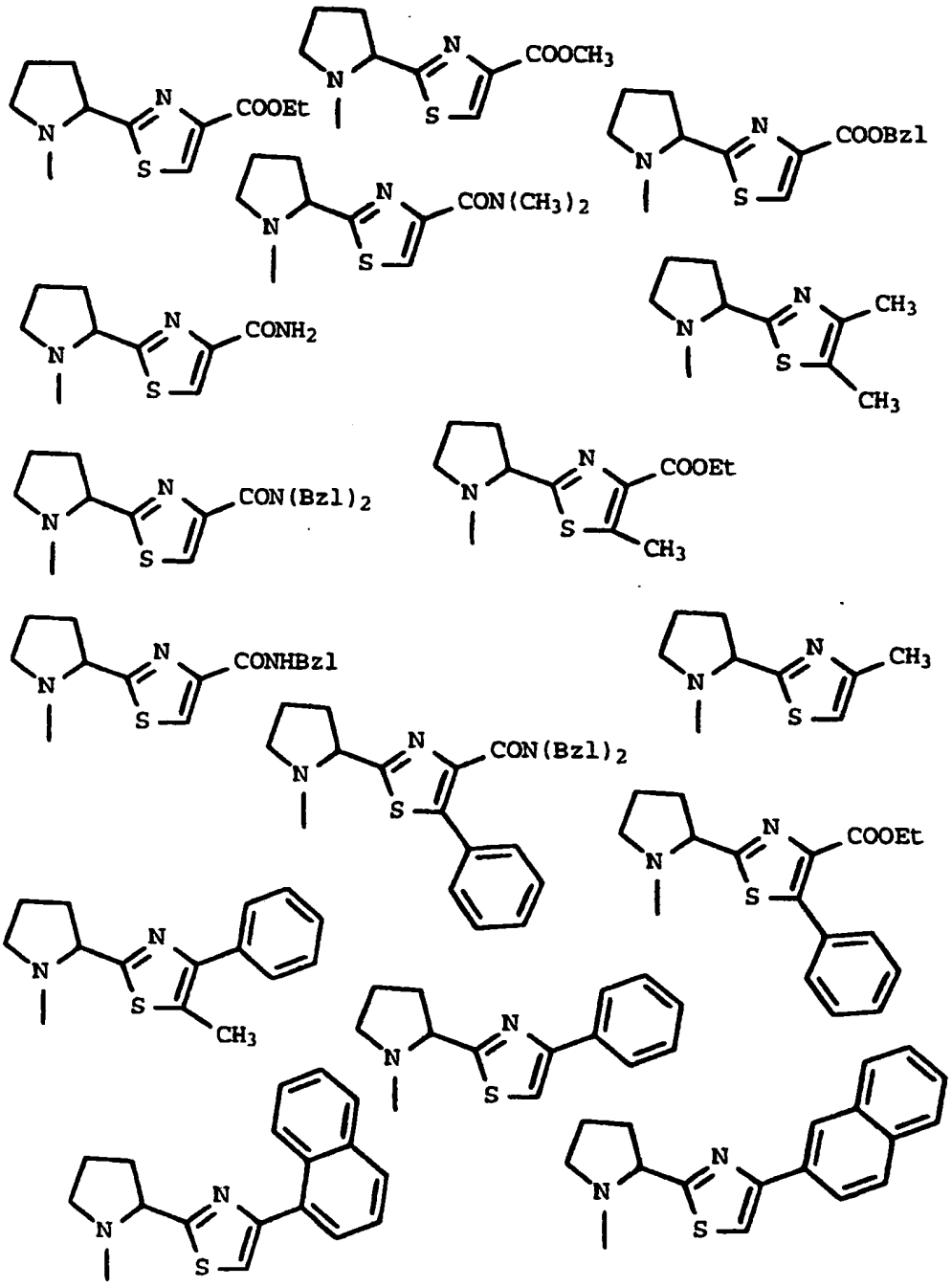

CH3
N
N
CH3
CH3
CH3



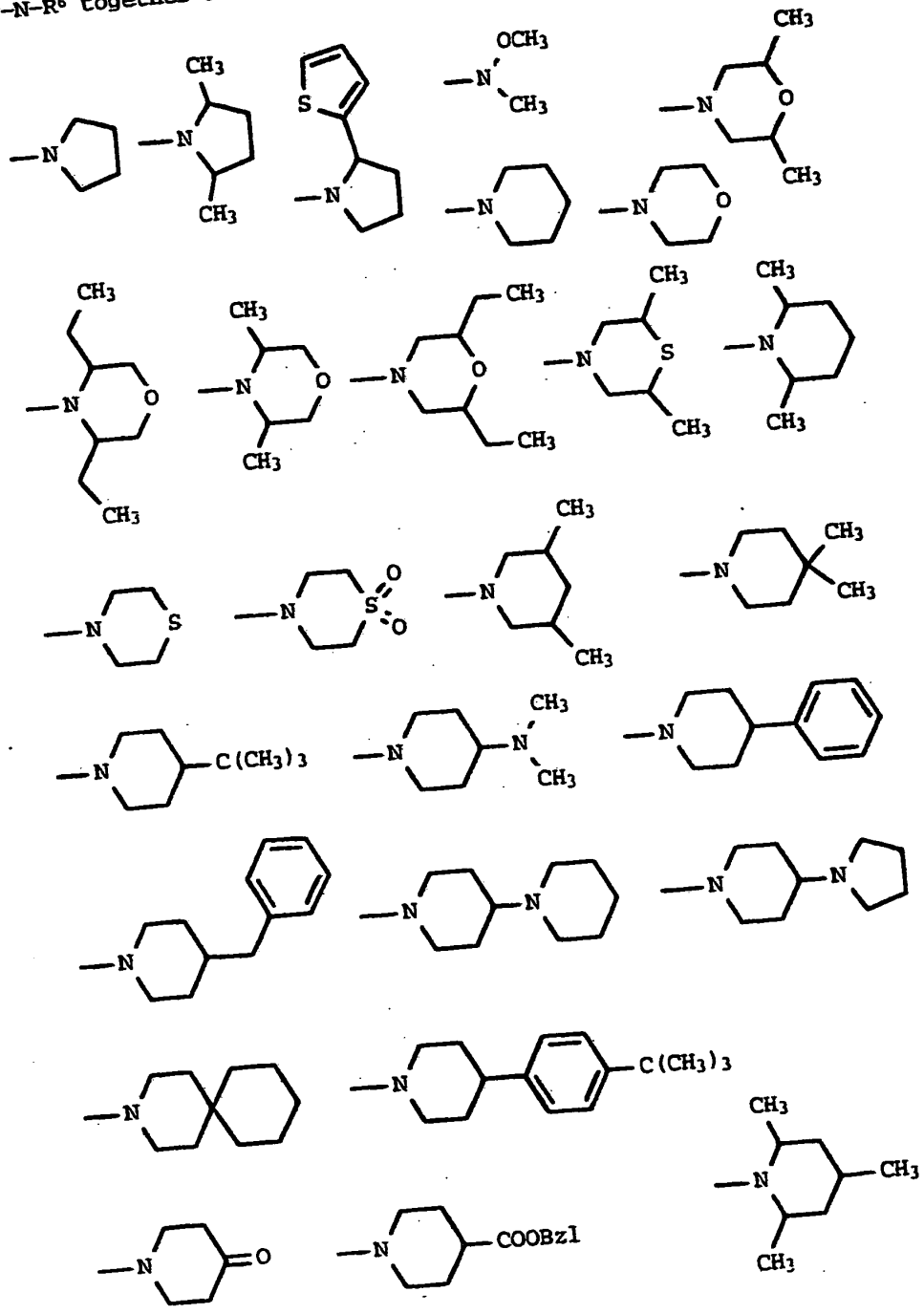

CN
F
F
NO2
NO2
OCH3
OCH3
CH3
CF3
F
OCH3
OEt
CH(CH3)2
C(CH3)3
O
O
CF3
CH3
CH3
CF3
CF3
OCH3
OCH3
OCH3
OCH3
OCH3
CF3

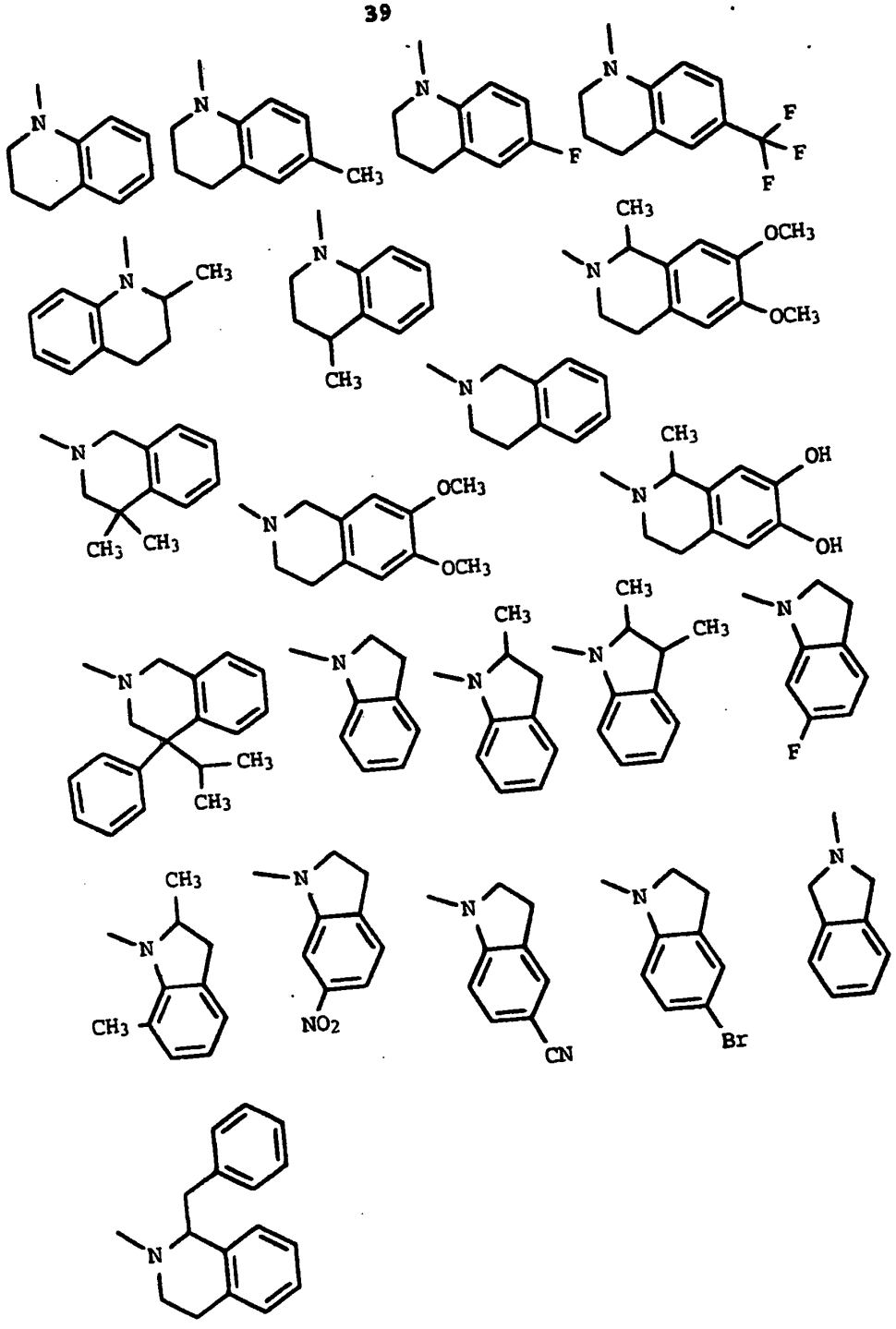

CH2
N
CH3
O
S
F
NH2

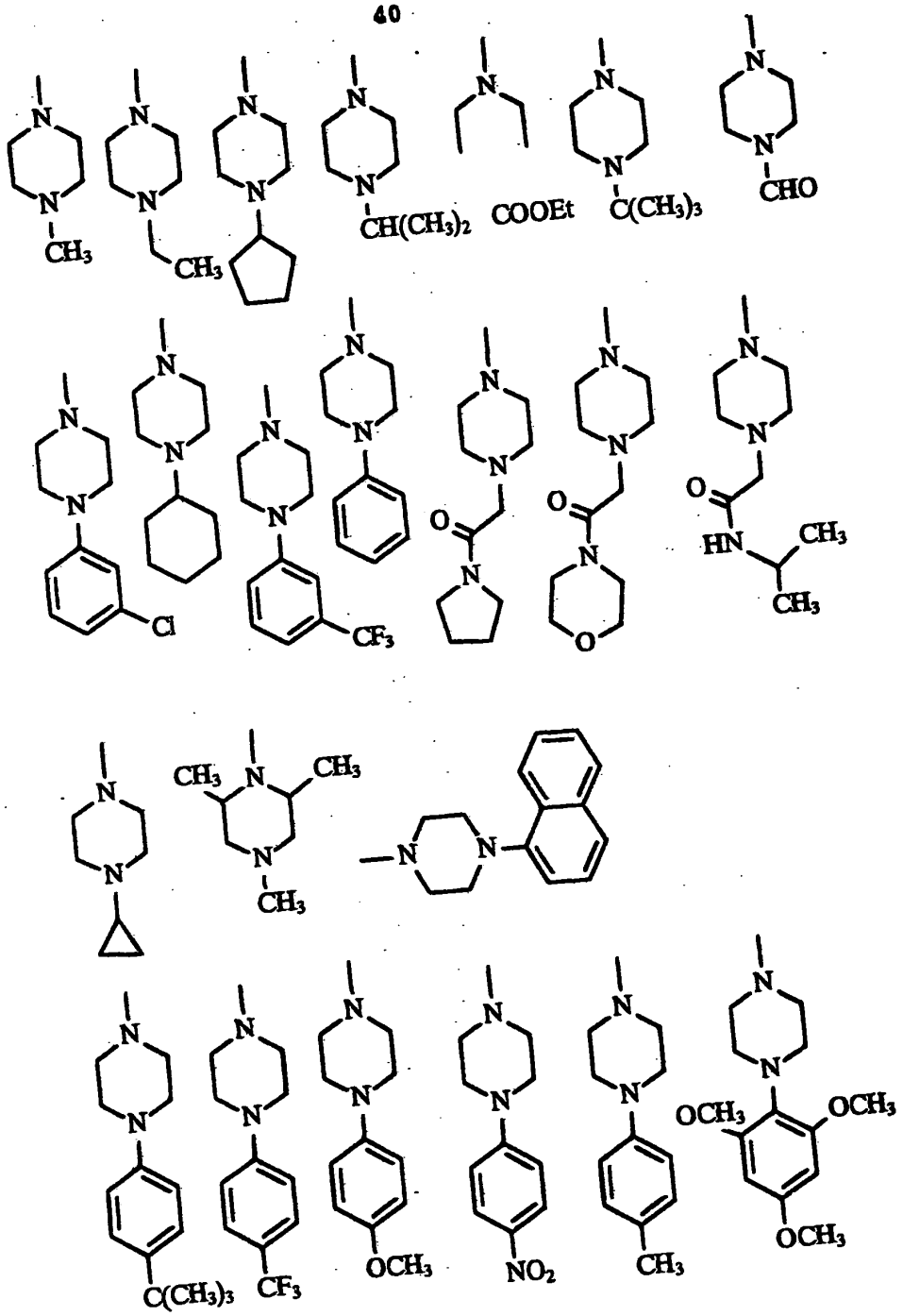
R^5-N-CHR^7-5-membered heteroaryl are

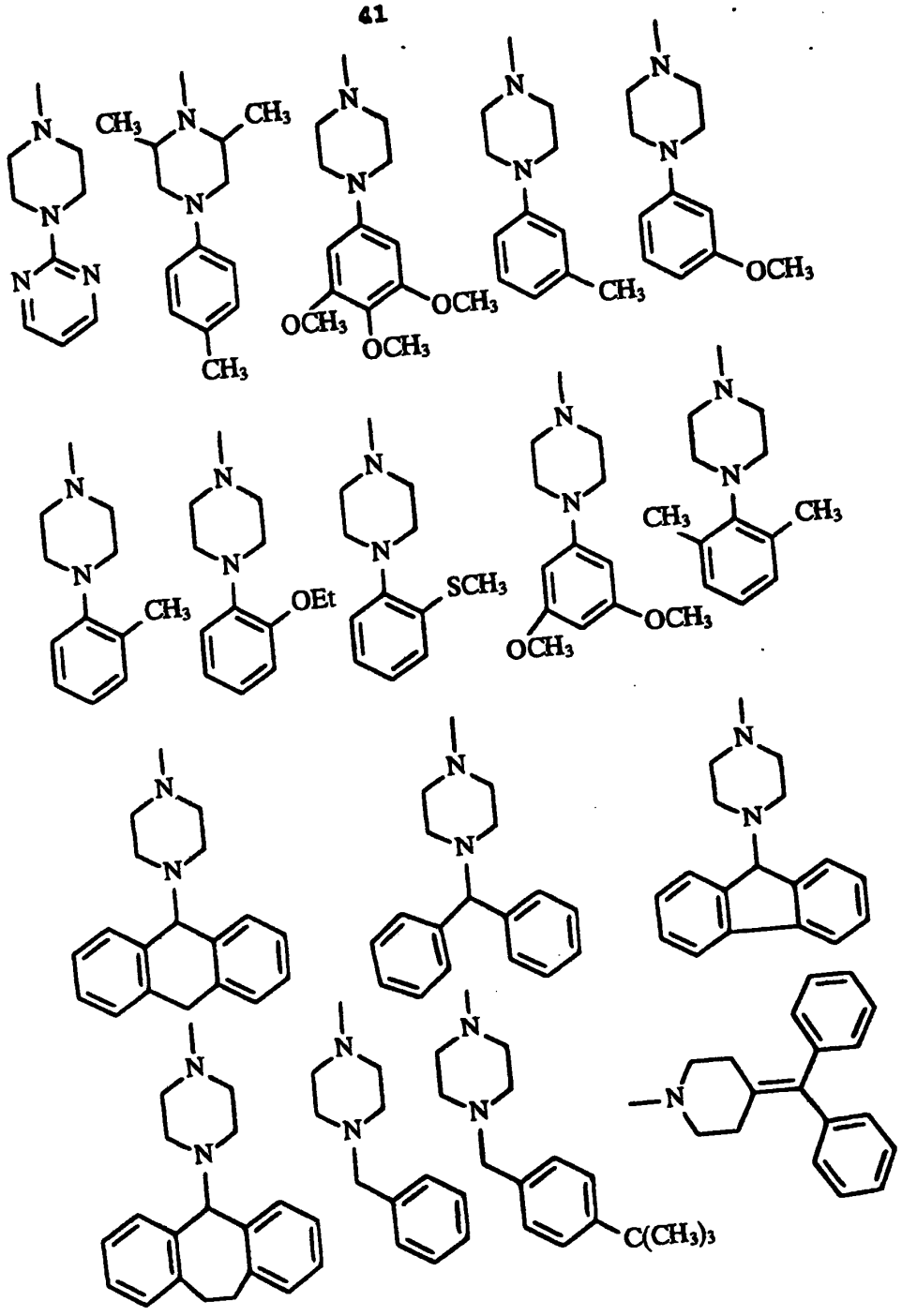


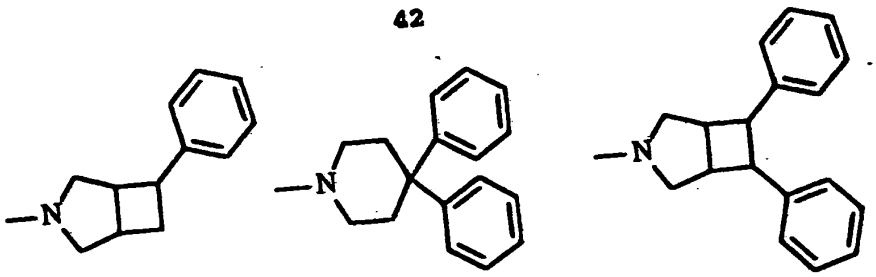
R^5–N–R^6 together are






CH3
CH3
CH(CH3)2
COOEt
C(CH3)3
CHO
Cl
CF3
O
O
HN
CH3
CH3
CH3
CH3
CH3
C(CH3)3
CF3
OCH3
NO2
CH3
OCH3
OCH3
OCH3





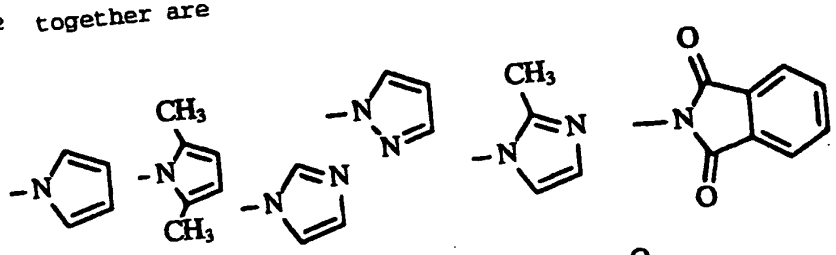
K is a hydroxy, alkoxy (preferably C_{1-4}), phenoxy or benzoxy moiety.

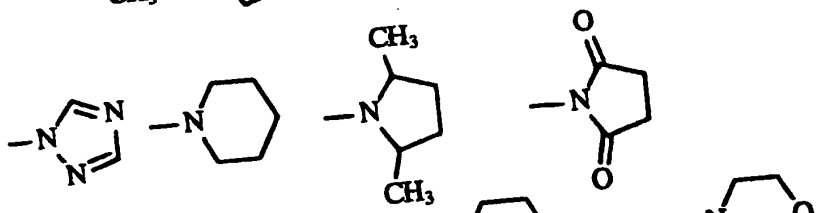
More preferred are compounds where the substituents have the following meanings:

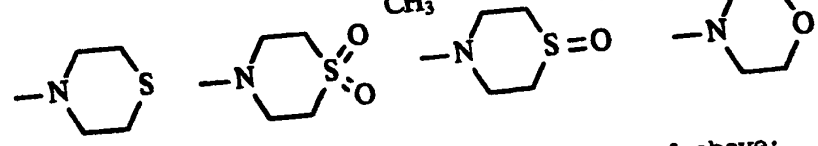
R^1 is ethyl, methyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-fluoroisopropyl, trifluoroisopropyl, isopropyl, propyl, cyclopropyl, benzyloxycarbonyl, methyloxycarbonyl, lactyl, methylaminosulfonyl,tosyl, ureyl, mesyl, $N(CH_3)_2$, amidino. methoxy, benzyl, 4-phenoxybenzyl, 4-benzyloxybenzyl, or 3,4,5-trimethoxybenzyl

R^2 is hydrogen, methyl, ethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, isopropyl, propyl, butyl, cyclopropyl, formyl, acetyl, propionyl, pivaloyl, benzoyl or benzyl,

R^1-N-R^2 together are



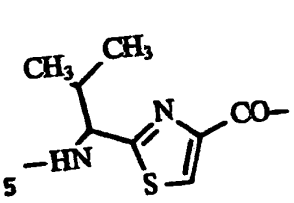


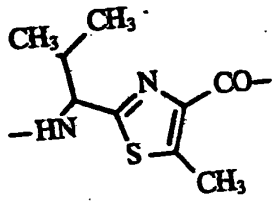


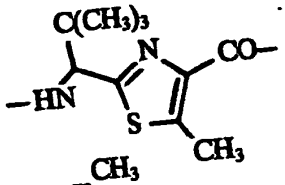
A, B, D, E, F, G and X have the meanings as described above;

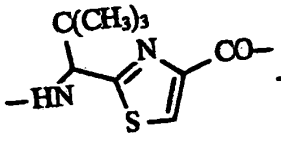
t, u, v and w are independently 0 or 1;

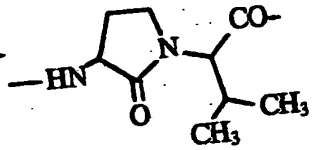
A and B together are

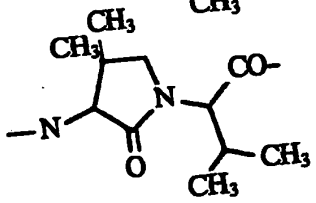


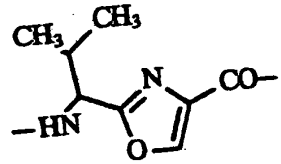


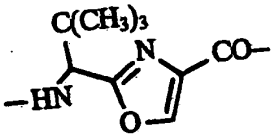


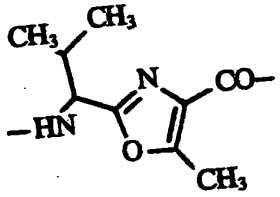


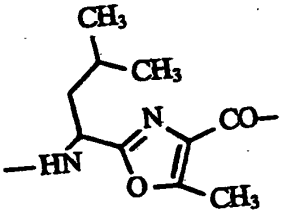


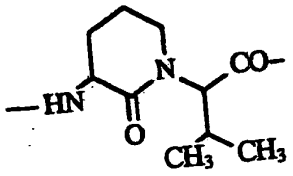


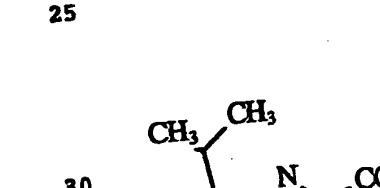


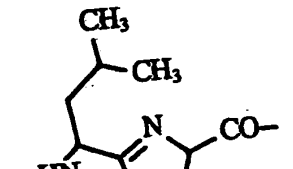


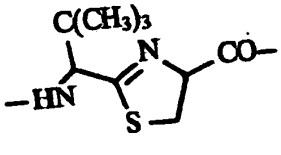


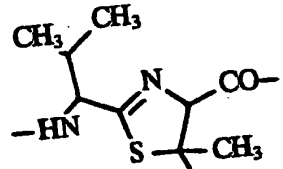


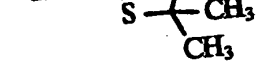


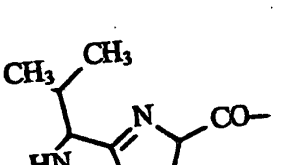


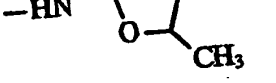


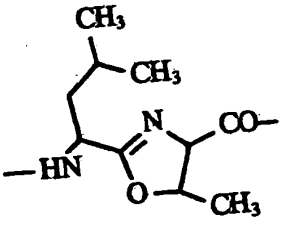


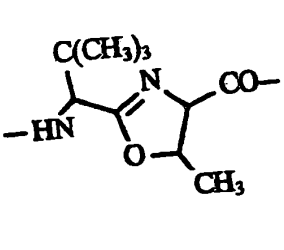




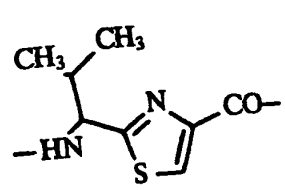


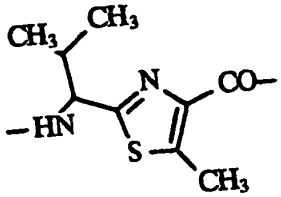


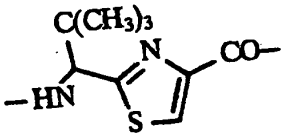


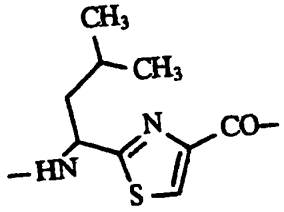


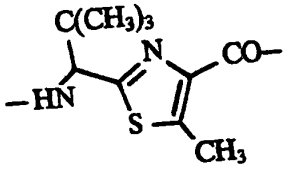
F and G together are

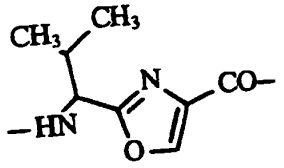


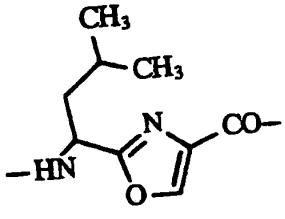


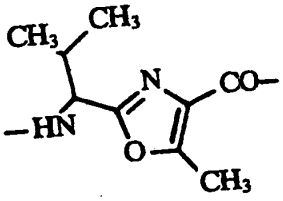


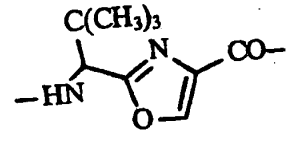


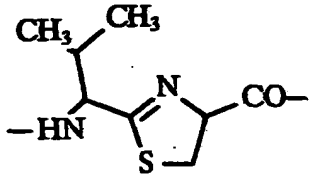


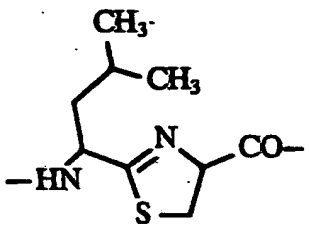


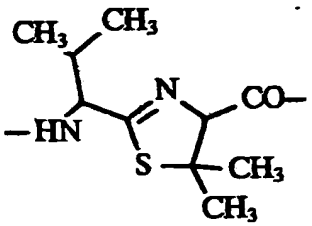


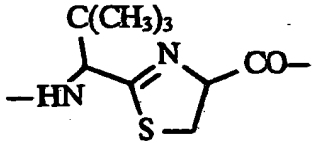


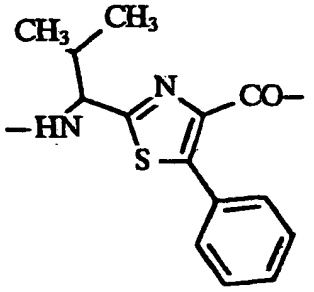


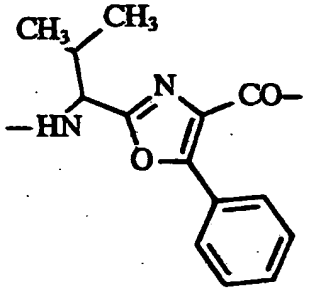


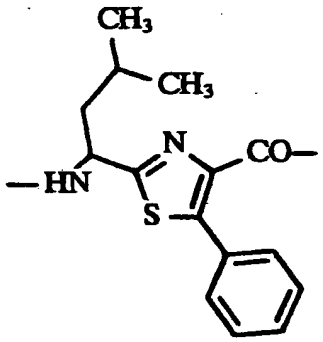


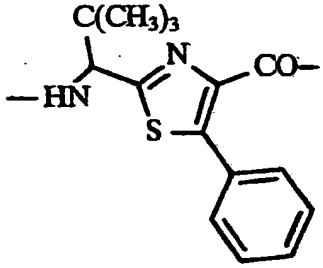


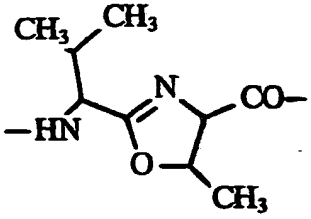


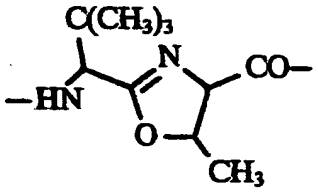




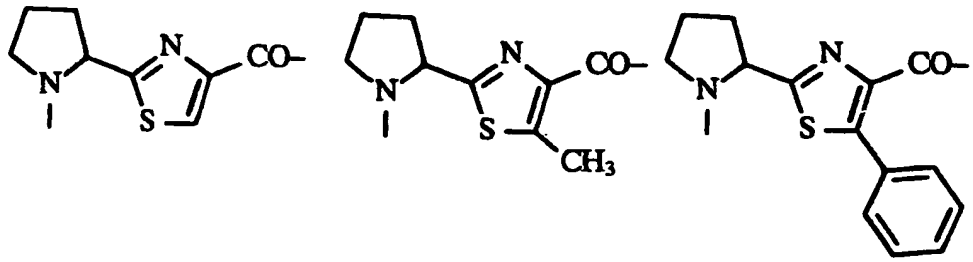




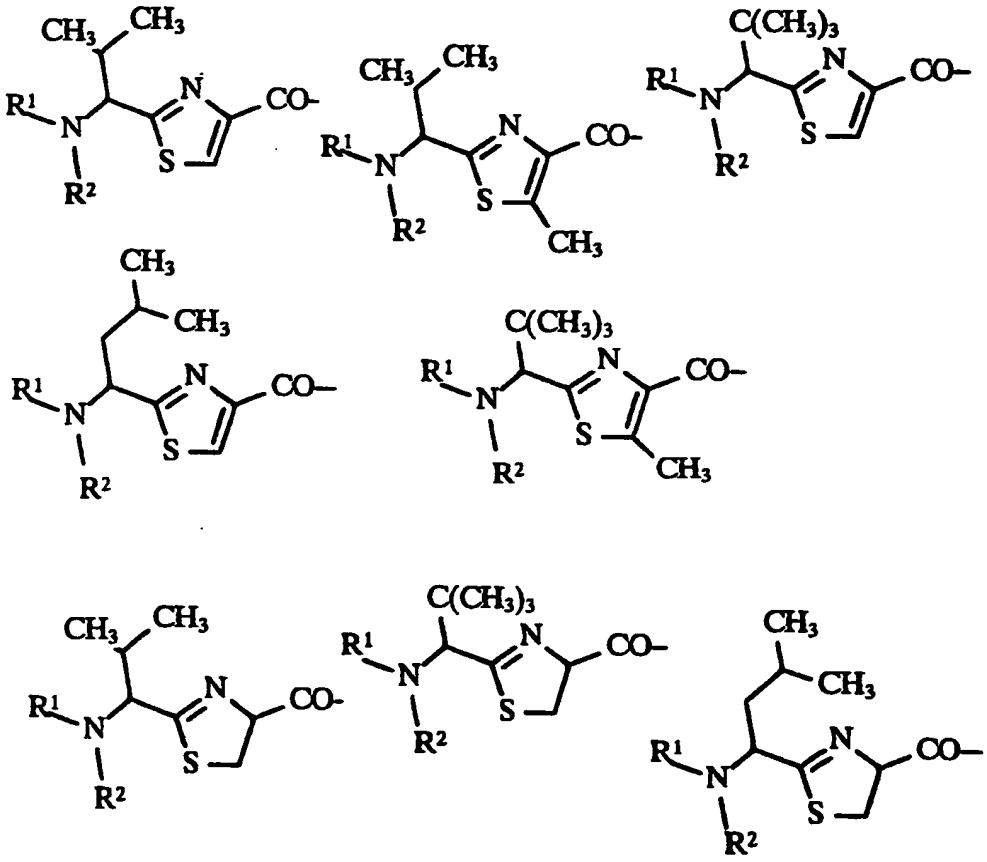


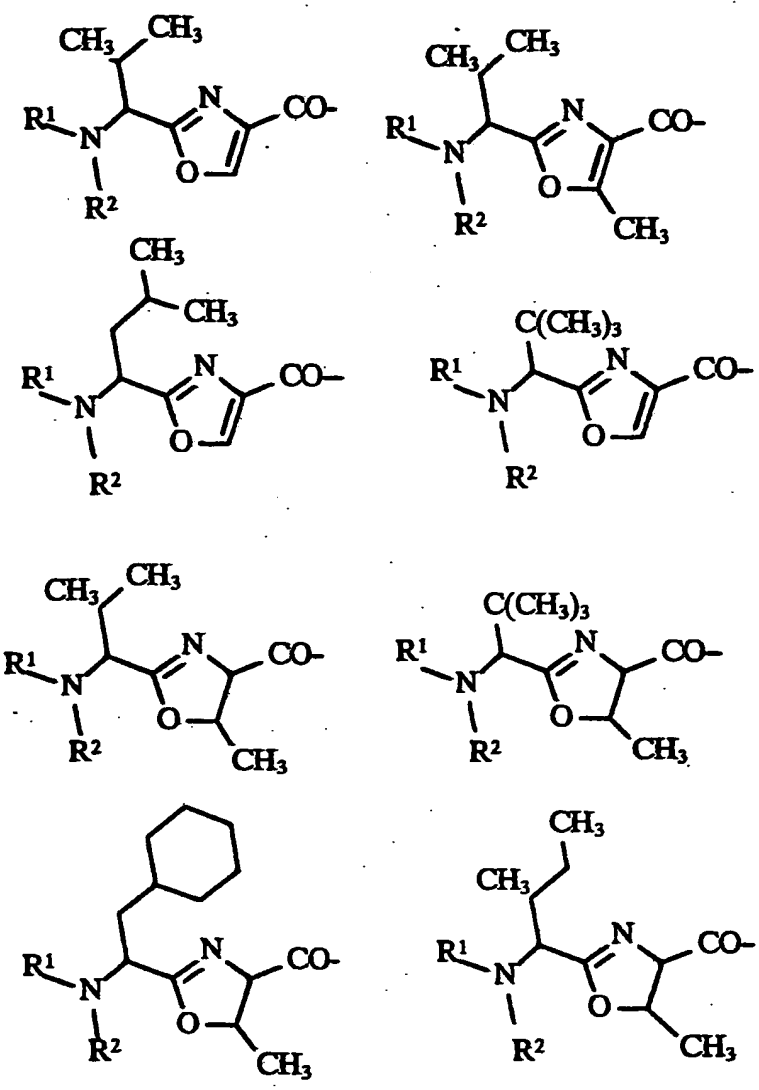


E and F together are



R^1R^2N-CHX-CO and A together are

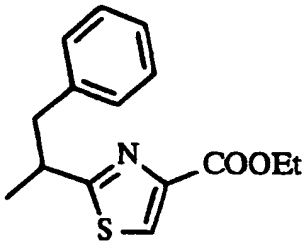


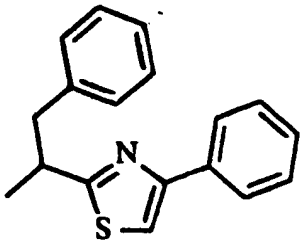


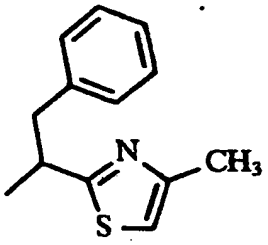
K is a hydroxy, C_{1-6}-alkoxy or benzyloxy moiety;

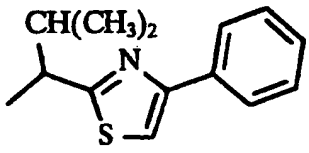
R^5 is hydrogen, methyl, ethyl, 2-fluoroethyl, 2,2-difluoroethyl, propyl, isoproypyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, 4-phenoxybenzyl, 4-benzyloxybenzyl or 3,4,5-trimethoxybenzyl

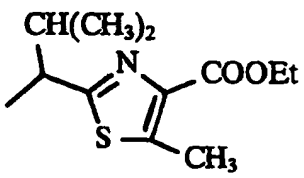
R^6 is hydrogen, methyl, ethyl, 2-fluoroethyl, 2,2-trifluoroethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, 4-phenoxybenzyl, 4-benzyloxybenzyl, 3,4,5-trimethoxybenzyl, phenyl, 4-phenoxyphenyl, 4-benzyloxyphenyl, 3,4,5-trimethoxyphenyl or

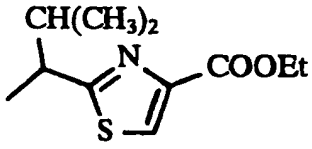

N
COOEt
S

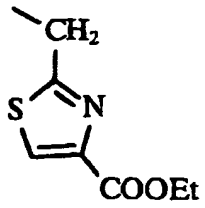

N
S

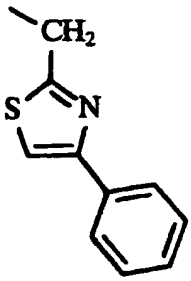

N
CH3
S

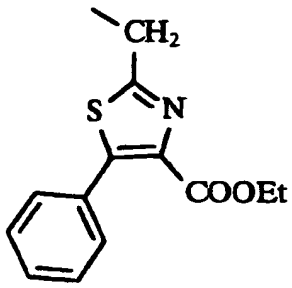

CH(CH3)2
N
S

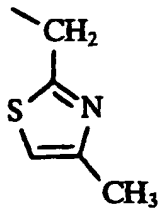

CH(CH3)2
N
COOEt
S
CH3

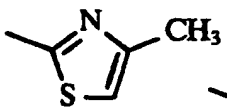

CH(CH3)2
N
COOEt
S

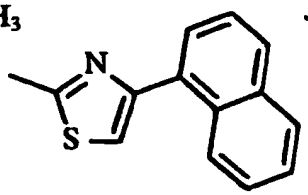

CH2
S
N
COOEt

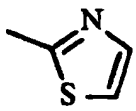

CH2
S
N

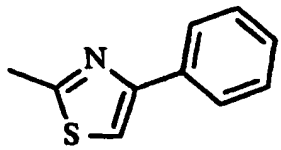

CH2
S
N
COOEt

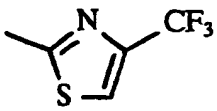

CH2
S
N
CH3

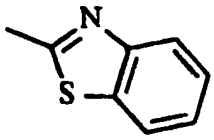

N
CH3
S

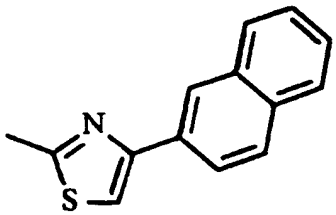

N
S

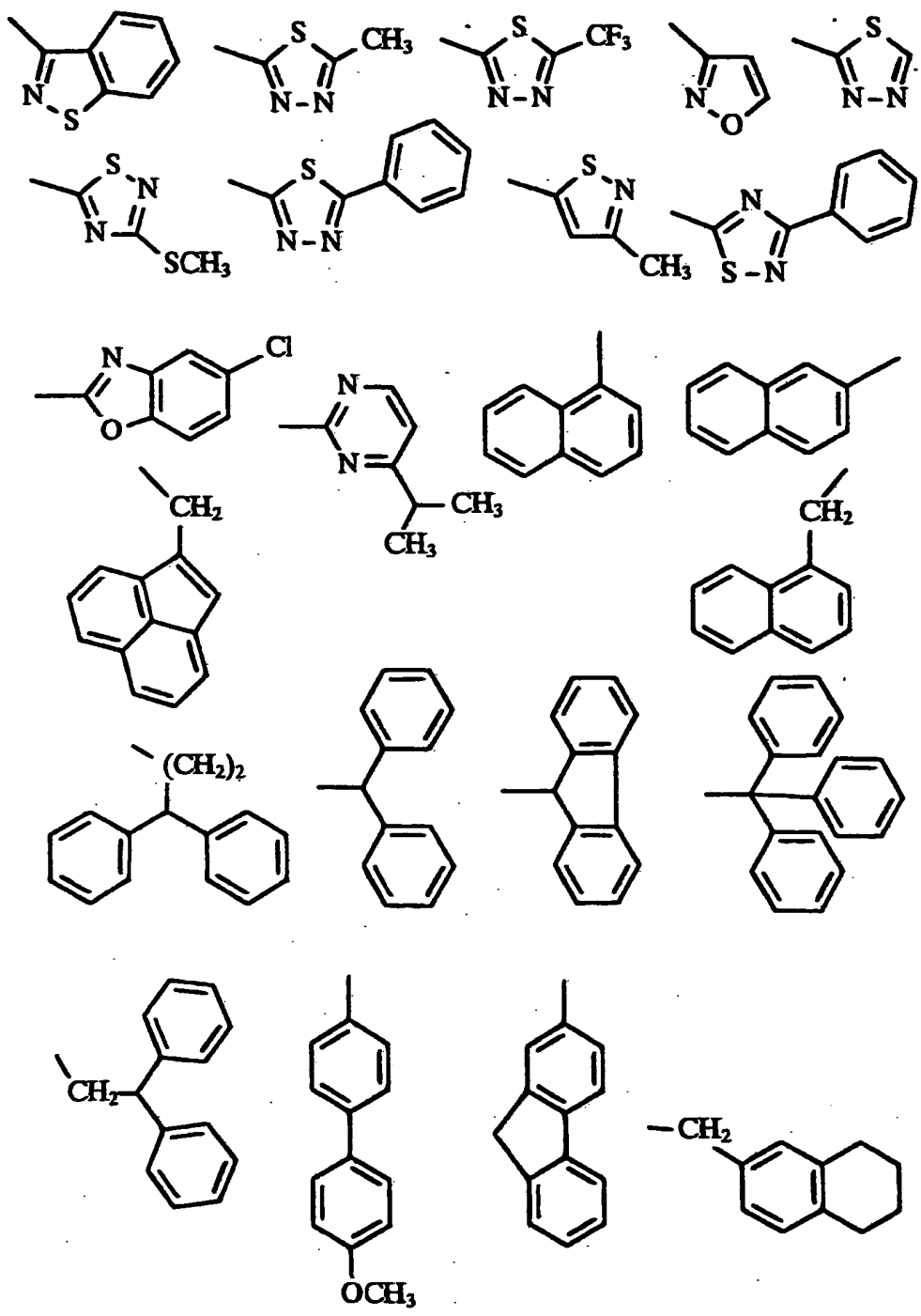

N
S

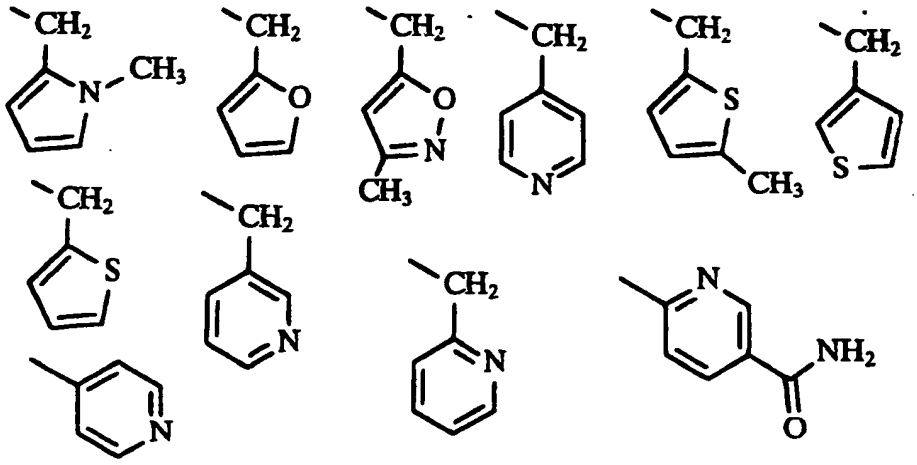

N
S


N
CF3
S

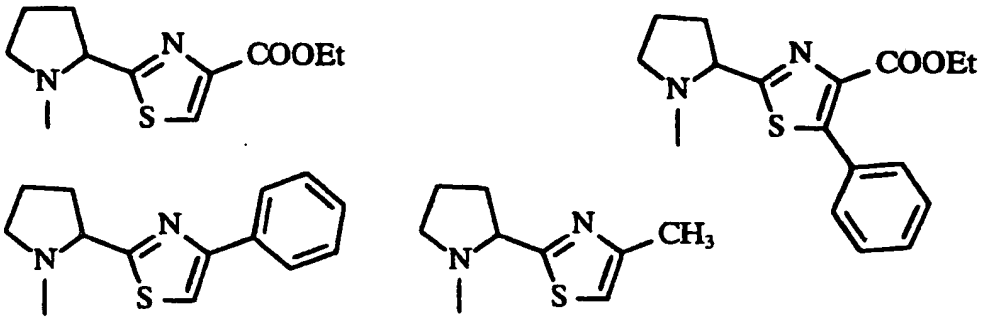

N
S


N
S

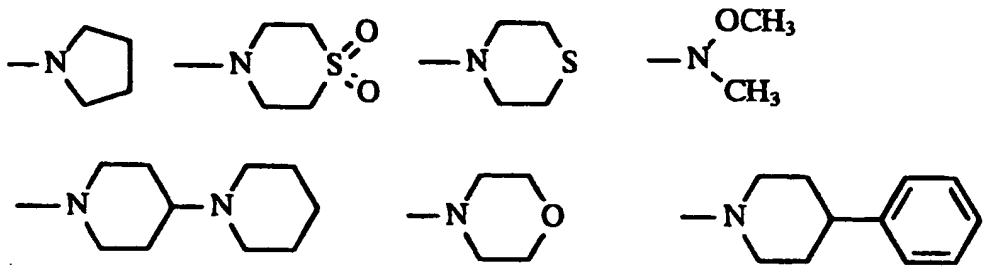


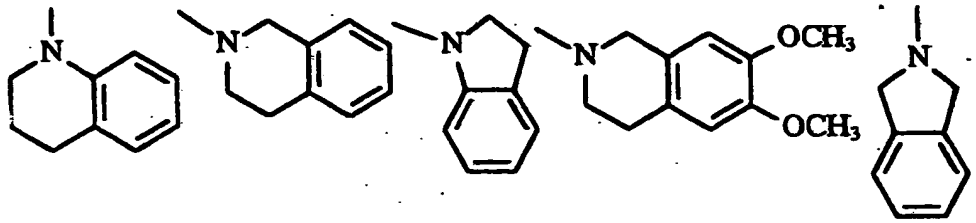


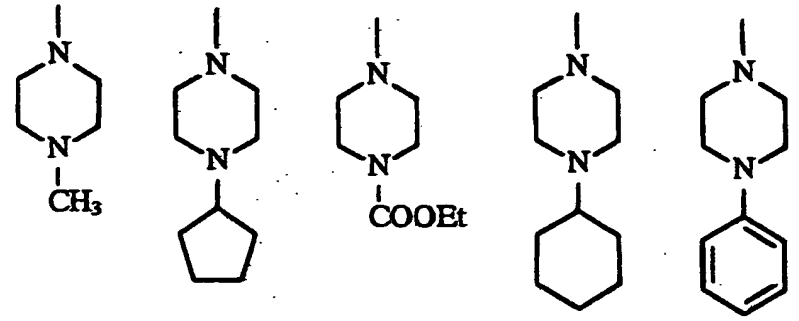
R^5-N-CHR^7-5-membered heteroaryl is

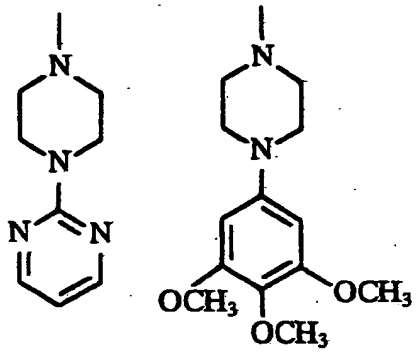


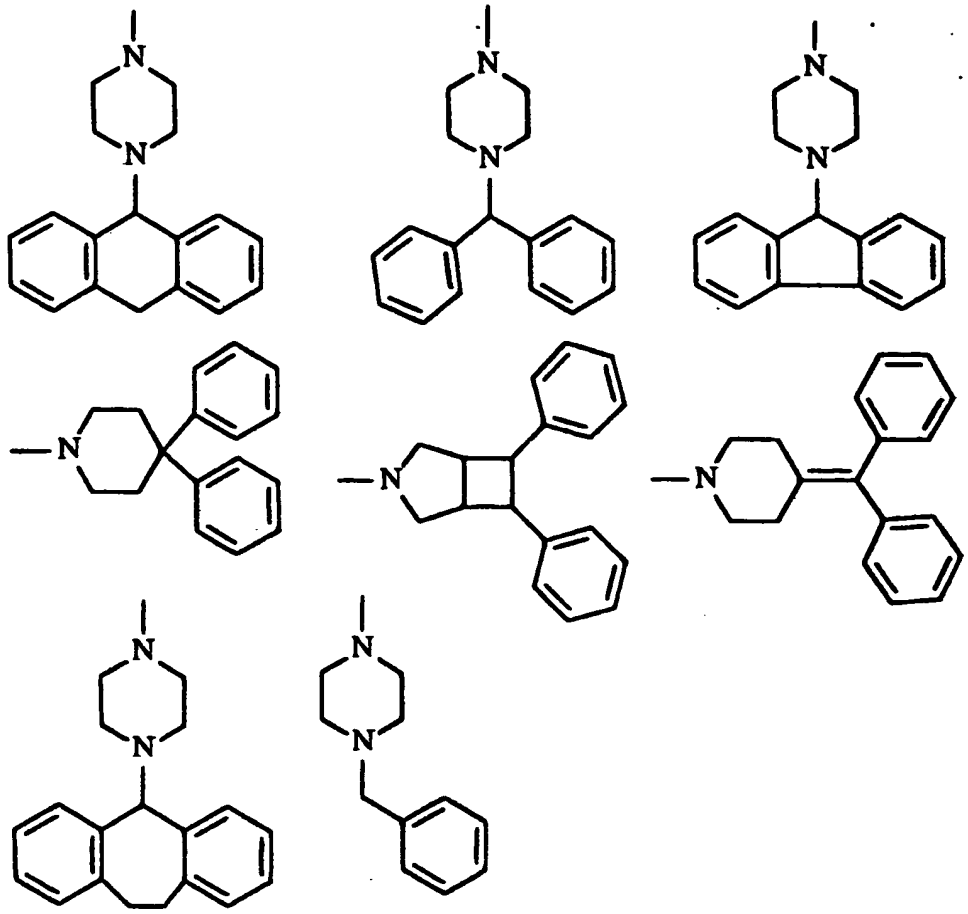
R^5-N-R^6 together are











These examples illustrate but do not limit the scope of the present invention.

The peptides of the formula I are composed preferably of L-amino acids but they may contain one or more D-amino acids.

The new compounds may be present as salts with physiologically tolerated acids such as: hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, malic acid, succinic acid, malonic acid, sulfuric acid, L-glutamic acid, L-aspartic acid, pyruvic acid, mucic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

The novel compounds can be prepared by known methods of peptide chemistry. Thus, the peptides can be assembled sequentially from amino acids or by linking suitable small peptide fragments. In the sequential assemblage, starting at the C terminus the peptide chain is extended stepwise by one amino acid each time. In fragment coupling it is possible to link together fragments of different lengths, and the fragments in turn can be obtained by sequential assemblage from amino acids or themselves by fragment coupling.

Both in the sequential assemblage and in the fragment coupling it is necessary to link the units by forming an amide linkage. Enzymatic and chemical methods are suitable for this.

Chemical methods for forming the amide linkage are described in detail by Müller, Methoden der organischen Chemie Vol. XV/2, pp 1 to 364, Thieme Verlag, Stuttgart, 1974; Stewart, Young, Solid Phase Peptide Synthesis, pp 31 to 34, 71 to 82, Pierce Chemical Company, Rockford, 1984; Bodanszky, Klausner, Ondetti, Peptide Synthesis, pp 85 to 128, John Wiley & Sons, New York, 1976 and other standard works on peptide chemistry. Particular preference is given to the azide method, the symmetric and mixed anhydride method, in situ generated or preformed active esters, the use of urethane protected N-carboxy anhydrides of amino acids and the formation of the amide linkage using coupling reagents (activators, especially dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), n-propanephosphonic anhydride (PPA), N,N-bis(2-oxo-3-oxazolidinyl)- midophosphoryl chloride (BOP-Cl), bromo-tris-pyrrolidinophosphonium hexa-fluorophosphate (PyBrop), diphenylphosphoryl azide (DPPA), Castro's reagent (BOP, PyBop),

O-benzotriazolyl-N,N,N',N'-tetramethyluronium salts (HBTU), diethylphosphoryl cyanide (DEPCN), 2,5-diphenyl-2,3-dihydro-3-oxo-4-hydroxythiophene dioxide (Steglich's reagent; HOTDO) and 1,1'-carbonyldiimidazole (CDI). The coupling reagents can be employed alone or in combination with additives such as N,N-dimethyl-4-aminopyridine (DMAP), N-hydroxy-benzotriazole (HOBt), N-hydroxybenzotriazine (HOOBt), N-hydroxysuccinimide (HOSu) or 2-hydroxypyridine.

Whereas it is normally possible to dispense with protective groups in enzymatic peptide synthesis, reversible protection of reactive groups not involved in formation of the amide linkage is necessary for both reactants in chemical synthesis. Three conventional protective group techniques are preferred for the chemical peptide synthesis: the benzyloxycarbonyl (Z), the t-butoxycarbonyl (Boc) and the 9-fluorenylmethoxycarbonyl (Fmoc) techniques. Identified in each case is the protective group on the α-amino group of the chain-extending unit. A detailed review of amino-acid protective groups is given by Müller, Methoden der organischen Chemie Vol. XV/1, pp 20 to 906, Thieme Verlag, Stuttgart, 1974. The units employed for assembling the peptide chain can be reacted in solution, in suspension or by a method similar to that described by Merrifield in J. Amer. Chem. Soc. 85 (1963) 2149. Particularly preferred methods are those in which peptides are assembled sequentially or by fragment coupling using the Z, Boc or Fmoc protective group technique, with one of the reactants in the said Merrifield technique being bonded to an insoluble polymeric support (also called resin hereinafter). This typically entails the peptide being assembled sequentially on the polymeric support using the Boc or Fmoc protective group technique, the growing peptide chain being covalently bonded at the C terminus to the insoluble resin particles (cf. Fig. 1 and 2). This procedure makes it possible to remove reagents and byproducts by filtration, and thus recrystallization of intermediates is unnecessary.

The protected amino acids can be linked to any suitable polymers, which merely have to be insoluble in the solvents used and to have a stable physical form which makes filtration easy. The polymer must contain a functional group to which the first protected amino acid can be firmly attached by a covalent bond. Suitable for this purpose are a wide variety of polymers, eg. cellulose, polyvinyl alcohol, polymethacrylate, sulfonated polystyrene, chloromethylated styrene/divinylbenzene copolymer (Merrifield resin), 4-methylbenzhydrylamine resin (MBHA-resin), phenylacetamidomethyl-resin (Pam-resin), p-benzyloxy-benzyl-alcohol-resin, benzhydryl-amine-resin (BHA-resin), 4-(hydroxyme-

thyl)benzoyloxy-methyl-resin, the resin of Breipohl et al. (Tetrahedron Letters 28 (1987) 565; supplied by BACHEM), 4-(2,4-dimethoxyphenylaminomethyl)phenoxy-resin (supplied by Novabiochem) or o-chlorotrityl-resin (supplied by Biohellas).

Suitable for peptide synthesis in solution are all solvents which are inert under the reaction conditions, especially water, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dichloromethane (DCM), 1,4-dioxane, tetrahydrofuran (THF), N-methyl-2-pyrrolidone (NMP) and mixtures of the said solvents. Peptide synthesis on the polymeric support can be carried out in all inert organic solvents in which the amino-acid derivatives used are soluble; however, preferred solvents additionally have resin-swelling properties, such as DMF, DCM, NMP, acetonitrile and DMSO, and mixtures of these solvents. After synthesis is complete, the peptide is cleaved off the polymeric support. The conditions under which cleavage off the various resin types is possible are disclosed in the literature. The cleavage reactions most commonly used are acid- and palladium-catalyzed, especially cleavage in liquid anhydrous hydrogen fluoride, in anhydrous trifluoromethanesulfonic acid, in dilute or concentrated trifluoroacetic acid, palladium-catalyzed cleavage in THF or THF-DCM mixtures in the presence of a weak base such as morpholine or cleavage in acetic acid/dichloromethane/trifluoroethanol mixtures. Depending on the chosen protective groups, these may be retained or likewise cleaved off under the cleavage conditions. Partial deprotection of the peptide may also be worthwhile when certain derivatization reactions are to be carried out. Peptides dialkylated at the N-terminus can be prepared either by coupling on the appropriate N,N-di-alkylamino acids in solution or on the polymeric support or by reductive alkylation of the resin-bound peptide in DMF/1% acetic acid with $NaCNBH_3$ and the appropriate aldehydes. The various non-naturally occurring amino acids as well as the various non-amino acid moieties disclosed herein may be obtained from commercial sources or synthesized from commercially-available materials using methods known in the art. For example, amino acids building blocks with R^1 and R^2 moieties can be prepared according to E. Wünsch, Houben Weyl, Meth. d. Org. Chemie, Bd. XV, 1, p. 306 following, Thieme Verlag Stuttgart 1974 and Literature cited therein. Peptides with γ- or δ-lactam bridges can be prepared by incorporating the appropriate lactam-bridged dipeptide units (R. Freidinger, J. Org. Chem. (1982) 104-109) into the peptide chain. Peptides with thiazole-, oxazol-, thiazolin- or oxazolin-containing dipeptide building blocks can be prepared by incorporating the appropriate dipeptidic units (P. Jouin et al., Tetrahedron Letters (1992), 2807-2810; P. Wipf et al., Tetrahedron Letters (1992), 907-910; W.R. Tully, J. Med.

Chem. (1991), 2065; Synthesis (1987), 235) into the peptide chain.

The compounds of this invention may be used to inhibit or otherwise treat solid tumors (e.g. tumors of the lung, breast, colon, prostate, bladder, rectum, or endometrial tumors) or hematological malignancies (e.g. leucemias, lymphomas) by administration of the compound to the mammal. Administration may be by any of the means which are conventional for pharmaceutical, preferably oncological, agents, including oral and parenteral means such as subcutaneously, intravenously, intramuscularly and intraperitoneally. The compounds may be administered alone or in the form of pharmaceutical compositions containing a compound of formula I together with a pharmaceutically accepted carrier appropriate for the desired route of administration. Such pharmaceutical compositions may be combination products, i.e., may also contain other therapeutically active ingredients.

The dosage to be administered to the mammal will contain an effective tumor-inhibiting amount of active ingredient which will depend upon conventional factors including the biological activity of the particular compound employed; the means of administration; the age, health and body weight of the recipient; the nature and extent of the symptoms; the frequency of treatment; the administration of other therapies; and the effect desired. A typical daily dose will be about 5 to 250 milligrams per kilogram of body weight on oral administration and about 1 to 100 milligrams per kilogram of body weight on parenteral administration.

The novel compounds can be administered in conventional solid or liquid pharmaceutical administration forms, eg. uncoated or (film-)coated tablets, capsules, powders, granules, suppositories or solutions. These are produced in a conventional manner. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, sustained release compositions, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The administration forms obtained in this way normally contain 1-90% by weight of the active substance.

The following examples are intended to illustrate the invention. The proteinogenous amino acids are abbreviated in the examples using the known three-letter code. Other meanings are: TFA = tri-

fluoroacetic acid, Ac = acetic acid, Bu = butyl, Et = ethyl, Me = methyl, Bzl = benzyl.

A. General procedures

I. The peptides claimed in claim 1 are either synthesized by classical solution synthesis using standard Z- and Boc-methodology as described above or by standard methods of solid-phase synthesis on a completely automatic model 431A synthesizer supplied by APPLIED BIOSYSTEMS. The apparatus uses different synthetic cycles for the Boc and Fmoc protective group techniques.

a) Synthetic cycle for the Boc protective group technique

1.	30% trifluoroacetic acid in DCM	1 x 3 min
2.	50% trifluoroacetic acid in DCM	1 x 1 min
3.	DCM washing	5 x 1 min
4.	5% diisopropylethylamine in DCM	1 x 1 min
5.	5% diisopropylethylamine in NMP	1 x 1 min
6.	NMP washing	5 x 1 min
7.	Addition of preactivated protected amino acid (activation with 1 equivalent of DCC and 1 equivalent of HOBt in NMP/DCM); Peptide coupling (1st part)	1 x 30 min
8.	Addition of DMSO to the reaction mixture until it contains 20% DMSO by volume	
9.	Peptide coupling (2nd part)	1 x 16 min
10.	Addition of 3.8 equivalents of diisopropylethylamine to the reaction mixture	
11.	Peptide coupling (3rd part)	1 x 7 min
12.	DCM washing	3 x 1 min
13.	if conversion is incomplete, repetition of coupling (back to 5.)	
14.	10% acetic anhydride, 5% diisopropylethylamine in DCM	1 x 2 min
15.	10% acetic anhydride in DCM	1 x 4 min
16.	DCM washing	4 x 1 min
17.	back to 1.	

BOP-Cl and PyBrop were used as reagents for coupling of the amino acid following N-methylamino acids. The reaction times were correspondingly increased. In solution synthesis, the use of either Boc-protected amino acid NCAs (N-tert.-butyloxycarbonyl-

amino acid-N-carboxy-anhydrides) or Z-protected amino acid NCAs (N-benzyloxycarbonyl-amino acid-N-carboxy-anhydrides) respectively is most advantageous for this type of coupling.

b) Synthetic cycle for the Fmoc protective group technique

1.	DMF washing	1 x 1 min
2.	20% piperidine in DMF	1 x 4 min
3.	20% piperidine in DMF	1 x 16 min
4.	DMF washing	5 x 1 min
5.	Addition of the preactivated protected amino acid (activation by 1 equivalent of TBTU and 1.5 equivalent of DIPEA in DMF); Peptide coupling	1 x 61 min
6.	DMF washing	3 x 1 min
7.	if conversion is incomplete, repetition of coupling (back to 5.)	
8.	10% acetic anhydride in DMF	1 x 8 min
9.	DMF washing	3 x 1 min
10.	back to 2.	

BOP-Cl and PyBrop were used as reagents for coupling on the amino acid following the N-methylamino acids. The reaction times were correspondingly increased.

II. Reductive alkylation of the N terminus

The peptide-resin prepared as in AIa or AIb was deprotected at the N terminus (steps 2-4 in AIb or 1-6 in AIa) and then reacted with a 3-fold molar excess of aldehyde or ketone in DMF/1% acetic acid with addition of 3 equivalents of $NaCNBH_3$. After reaction was complete (negative Kaiser test) the resin was washed several times with water, isopropanol, DMF and dichloromethane.

III. Workup of the peptide-resins obtained as in Ia and II

The peptide-resin was dried under reduced pressure and transferred into a reaction vessel of a TEFLON HF apparatus (supplied by PENINSULA). Addition of a scavenger, preferably anisole (1 ml/g of resin), and in the case of tryptophan-containing peptides of a thiol to remove the indolic formyl group, preferably ethanedithiol (0.5 ml/g of resin), was followed by condensing in hydrogen fluoride (10 ml/g of resin) while cooling with liquid N_2. The mixture was left to warm to 0°C and stirred at this temperature for 45 min. The hydrogen fluoride was then stripped off under reduced pressure, and the residue was washed with ethyl acetate in

order to remove remaining scavenger. The peptide was extracted with 30% strength acetic acid and filtered, and the filtrate was lyophilized.

IV. Work-up of the peptide-resins obtained as in Ib and II

The peptide-resin was dried under reduced pressure and then subjected to one of the following cleavage procedures, depending on the amino-acid composition (Wade, Tregear, Howard Florey Fmoc Workshop Manual, Melbourne 1985).

	Cleavage conditions		
	TFA	Scavenger	Reaction time
1	95%	5% H2O	1.5 h
2	95%	5% ethanedithiol/anisol (1:3)	1,5 h

The suspension of the peptide-resin in the suitable TFA mixture was stirred at room temperature for the stated time and then the resin was filtered off and washed with TFA and DCM. The filtrate and the washings were concentrated, and the peptide was precipitated by addition of diethyl ether. After cooling in an ice bath, the precipitate was filtered off, taken up in 30% acetic acid and lyophilized.

V. When an o-chlorotrityl-resin (supplied by Biohellas) is used, the suspension of the peptide-resin in an acetic acid/trifluoroethanol/dichloromethane mixture (1:1:3) is stirred at room temperature for 1 h. The resin is then filtered off with suction and thoroughly washed with the cleavage solution. The combined filtrates are concentrated in acuo and treated with water. The precipitated solid is removed by filtration or centrifugation, washed with diethyl ether and dried under reduced pressure.

VI. Purification and characterization of the peptides

Purification was carried out by gel chromatography (SEPHADEX G-10, G-15/10% HOAc, SEPHADEX LH20/MeOH) with or without subsequent medium pressure chromatography (stationary phase: HD-SIL C-18, 20-45 µ, 100 Å; mobile phase: gradient with A = 0.1% TFA/MeOH, B = 0.1% TFA/H_2O).

The purity of the resulting products was determined by analytical HPLC (stationary phase: 100 2.1 mm VYDAC C-18, 5 1, 300 Å; mobile phase: CH_3CN/H_2O gradient, buffered with 0.1% TFA, 40°C). Characterization was by amino-acid analysis and fast atom bombardment mass spectroscopy.

B. Specific procedures

EXAMPLE 1 (SEQ ID NO: 1)

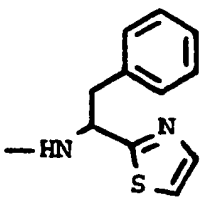
N,N-Dimethyl-Val-Val-N-methyl-Val-Pro-Pro-Val-Phe-NH_2

1.98 g of Fmoc-RINK-resin (substitution 0.46 mmol/g), corresponding to a batch size of 0.84 mmol, were reacted as in AIb with 1.26 mmol each of

Fmoc-Phe-OH	Fmoc-N-methyl-Val-OH
Fmoc-Val-OH	Fmoc-Val-OH
Fmoc-Pro-OH	Fmoc-Val-OH
Fmoc-Pro-OH	

The amino acid following the N-methylamino acid was coupled on with PyBrop as coupling reagent. After the iterative synthetic cycles were completed, the peptide-resin underwent N-terminal deprotection (steps 2-4 in AIb), and was further reacted with aqueous formaldehyde solution as in AII and then dried under reduced pressure. The resulting resin was subjected to TFA cleavage as in AIV. The crude product (590 mg) was purified by gel filtration (SEPHADEX-LH-20). The yield was 295 mg.

EXAMPLE 2 (SEQ ID NO: 2)

N,N-Dimethyl-Val-Val-N-Me-Val-Pro 

4.11 g of Fmoc-Pro-p-alkoxybenzyl-alcohol-resin (substitution 0.73 mmol/g), corresponding to a batch size of 3 mmol, were reacted as in AIb with 4.5 mmol each of

Fmoc-N-MeVal-OH
Fmoc-Val-OH
Fmoc-Val-OH.

The amino acid following the N-methylamino acid was in this case reacted with double coupling using PyBrop or Bop-Cl with increased reaction times. After the synthesis was complete, the peptide-resin underwent N-terminal deprotection (steps 2-4 in AIb), and was further reacted with aqueous formaldehyde solution as in AII and then dried under reduced pressure. The resin obtained in this way was subjected to TFA cleavage as in AIV. The crude product (750 mg) was employed directly for the next coupling. 100 mg of this compound were reacted with 45 mg of (S)-2-[1-amino-2-phenylethyl]thiazole and 230 mg of PyBop with the addition of 192 µl of DIPEA in DMF at room temperature for 2 d. The reaction mixture was purified by gel chromatography (Sephadex LH-20, methanol) and the product fractions were combined. 83 mg of product were obtained.

The following compounds were prepared and can be prepared according to examples 1 and 2:

3. Kaa Val Xan Pro Pro Val Phe
4. Kaa Val Xan Pro Pro Val Xac
5. Kaa Val Xan Pro Pro Val Xad
6. Kaa Val Xan Pro Pro Val Xae
7. Kaa Val Xan Pro Pro Val Xaf
8. Kaa Val Xan Pro Pro Val His-NH_2
9. Kbo Val Xan Pro Pro Val Phe-NH_2
10. Kaa Val Xan Pro Pro Val Xag-NH_2
11. Kaa Val Xan Pro Pro Val Xah
12. Kaa Xbe Xan Pro Pro Val Trp-NH_2
13. Kaa Val Xan Pro Pro Xai Phe-NH_2
14. Xae Val Xan Pro Pro Ile Phe-NH_2
15. Kaa Val Xan Pro Xal Val Phe-NH_2
16. Kaa Val Xan Pro Xak Val Phe-NH_2
17. Kaa Val Xan Xak Pro Val Phe-NH_2
18. Kaa Val Xan Xal Pro Val Phe-NH_2
19. Kaa Val Xao Pro Pro Val Phe-NH_2
20. Kaa Val Xam Pro Pro Val Phe-NH_2
21. Kaa Xap Pro Pro Val Phe-NH_2
22. Kaa Xaq Pro Pro Val Phe-NH_2
23. Kaa Ile Xan Pro Pro Val Phe-NH_2
24. Kaa Xai Xan Pro Pro Val Phe-NH_2
25. Kaa Leu Xan Pro Pro Val Phe-NH_2
26. Xar Val Xan Pro Pro Val Phe-NH_2
27. Xas Val Xan Pro Pro Val Phe-NH_2
28. Xat Val Xan Pro Pro Val Phe-NH_2
29. Xau Val Xan Pro Xal Val Phe-NH_2
30. Xav Val Xan Pro Pro Val Phe-NH_2
31. Xan Val Xan Pro Pro Val Phe-NH_2

32. Xaw Val Xan Pro Pro Val Phe-NH_2
33. Xax Val Xan Pro Pro Val Phe-NH_2
34. Xaa Val Xan Pro Pro Phe Phe-NH_2
35. Xaz Val Xan Pro Pro Val Phe-NH_2
36. Xba Val Xan Pro Pro Val Phe-NH_2
37. Xaa Val Xan Pro Pro Val-NH_2
38. Xaa Val Xan Pro Xbb
39. Xaa Val Xan Pro Xbc
40. Xaa Val Xan Pro Pro Xbd
41. Xax Val Xan Pro Pro Val-NH_2
42. Xaw Val Xan Pro Pro Val-NH_2
43. Xat Val Xan Pro Pro Val-NH_2
44. Xaa Xai Xan Pro Pro Val-NH_2
45. Xaa Val Xan Pro Pro Xai-NH_2
46. Xaa Val Xan Xak Pro Val-NH_2
47. Xaa Val Xan Pro Xak Val-NH_2
48. Xaa Val Xan Pro Pro Val
49. Xav Val Xan Pro Pro Val-NH_2
50. Xaa Val Xan Pro Pro-NH_2
51. Xaa Val Xan Pro Pro
52. Xaa Val Xan Pro Xbf
53. Xaa Val Xan Xbb
54. Xaa Val Xan Xbc
55. Xaa Val Xan Xbg
56. Xaa Val Xan Xbh
57. Xaa Val Xan Xbi
58. Xaa Val Xan Xbk
59. Xaa Val Xan Xbl
60. Xaa Val Xan Xbm
61. Xaa Val Xan Xbn
62. Xax Val Xan Pro Pro-NH_2
63. Xaw Val Xan Pro Pro-NH_2
64. Xbo Val Xan Pro Pro-NH_2
65. Xat Val Xan Pro Pro-NH_2
66. Xaa Xai Xan Pro Pro-NH_2
67. Xat Xai Xan Pro Pro-NH_2
68. Xaa Xap Pro Pro-NH_2
69. Xaa Xaq Pro Pro-NH_2
70. Xav Val Xan Pro Pro-NH_2
71. Xaa Xap Pro-NH_2
72. Xaa Xaq Pro-NH_2
73. Xaa Val Xan Pro
74. Xaa Val Xbp
75. Xaa Val Xbq
76. Xaa Val Xbr
77. Xaa Val Xbs
78. Xaa Val Xan Xbf

79. Xaa Val Xbt
80. Xaa Val Xbu
81. Xaa Val Xbv
82. Xaa Val Xbw
83. Xax Val Xan Pro-NH_2
84. Xbo Val Xan Pro-NH_2
85. Xav Val Xan Pro-NH_2
86. Xaa Val Xan Pro Xbn
87. Xaa Val Xan Pro Xbg
88. Xaa Val Xan Pro Xbi
89. Xaa Val Xan Pro Xbl
90. Xbo Val Xan Pro Xbg
91. Xbo Val Xan Pro Xbl
92. Xbo Xbe Xan Pro Xbg
93. Xaa Val Xan Pro Xbx
94. Xaa Xbe Xan Pro Pro-NH_2
95. Xby Val Xan Pro Pro Val Phe NH_2
96. Xed Val Xan Pro Pro Val Phe NH_2
97. Xee Val Xan Pro Pro Val Phe NH_2
98. Xef Val Xan Pro Pro Val Phe NH_2
99. Xbz Val Xan Pro Pro Val Phe NH_2
100. Xeg Val Xan Pro Pro Val Phe NH_2
101. Xca Val Xan Pro Pro Val Phe NH_2
102. Xcb Val Xan Pro Pro Val Phe NH_2
103. Xcb Val Xao Pro Pro Val Phe NH_2
104. Xcc Val Xan Pro Pro Val Phe NH_2
105. Xce Val Xan Pro Pro Val Phe NH_2
107. Xcg Val Xan Pro Pro Val Phe NH_2
108. Xch Val Xan Pro Pro Val Phe NH_2
109. Xci Val Xan Pro Pro Val Phe NH_2
110. Xck Val Xan Pro Pro Val Phe NH_2
111. Xcl Val Xan Pro Pro Val Phe NH_2
112. Xcm Val Xan Pro Pro Val Phe NH_2
113. Xcn Val Xan Pro Pro Val Phe NH_2
114. Xhn Val Xan Pro Pro Val Phe NH_2
115. Xho Val Xan Pro Pro Val Phe NH_2
116. Xhp Val Xan Pro Pro Val Phe NH_2
117. Xhq Val Xan Pro Pro Val Phe NH_2
118. Xby Val Xan Pro Pro Val NH_2
119. Xed Val Xan Pro Pro Val NH_2
120. Xee Val Xan Pro Pro Val NH_2
121. Xef Val Xan Pro Pro Val NH_2
122. Xbz Val Xan Pro Pro Val NH_2
123. Xeg Val Xan Pro Pro Val NH_2
124. Xca Val Xan Pro Pro Val NH_2
125. Xcb Val Xan Pro Pro Val NH_2
126. Xcc Val Xan Pro Pro Val NH_2

127. Xce Val Xan Pro Pro Val NH_2
128. Xcg Val Xan Pro Pro Val NH_2
129. Xch Val Xan Pro Pro Val NH_2
130. Xci Val Xan Pro Pro Val NH_2
131. Xck Val Xan Pro Pro Val NH_2
132. Xcl Val Xan Pro Pro Val NH_2
133. Xcm Val Xan Pro Pro Val NH_2
134. Xcn Val Xan Pro Pro Val NH_2
135. Xhn Val Xan Pro Pro Val NH_2
136. Xho Val Xan Pro Pro Val NH_2
137. Xhp Val Xan Pro Pro Val NH_2
138. Xhq Val Xan Pro Pro Val NH_2
139. Xby Val Xan Pro Pro NH_2
140. Xed Val Xan Pro Pro NH_2
141. Xee Val Xan Pro Pro NH_2
142. Xef Val Xan Pro Pro NH_2
143. Xbz Val Xan Pro Pro NH_2
144. Xeg Val Xan Pro Pro NH_2
145. Xca Val Xan Pro Pro NH_2
146. Xcb Val Xan Pro Pro NH_2
147. Xcc Val Xan Pro Pro NH_2
148. Xce Val Xan Pro Pro NH_2
149. Xcg Val Xan Pro Pro NH_2
150. Xch Val Xan Pro Pro NH_2
151. Xci Val Xan Pro Pro NH_2
152. Xck Val Xan Pro Pro NH_2
153. Xcl Val Xan Pro Pro NH_2
154. Xcm Val Xan Pro Pro NH_2
155. Xcn Val Xan Pro Pro NH_2
156. Xhn Val Xan Pro Pro NH_2
157. Xho Val Xan Pro Pro NH_2
158. Xhp Val Xan Pro Pro NH_2
159. Xhq Val Xan Pro Pro NH_2
160. Xaa Val Xan Pro Pro Val Xei
161. Xaa Val Xan Pro Pro Val Xem
162. Xaa Val Xan Pro Pro Val Xeo
163. Xaa Val Xan Pro Pro Val Xep
164. Xaa Val Xan Pro Pro Val Xeq
165. Xaa Val Xan Pro Pro Val Xex
166. Xaa Val Xan Pro Pro Val Xey
167. Xaa Val Xan Pro Pro Val Xfb
168. Xaa Val Xan Pro Pro Val Xfe
169. Xaa Val Xan Pro Pro Val Xfh
170. Xaa Val Xan Pro Pro Val Xfu
171. Xaa Val Xan Pro Pro Val Xfv
172. Xaa Val Xan Pro Pro Val Xft
173. Xaa Val Xan Pro Pro Val Xfw

174. Xaa Val Xan Pro Pro Val Xfx
175. Xaa Val Xan Pro Pro Val Xga
176. Xaa Val Xan Pro Pro Val Xgd
177. Xaa Val Xan Pro Pro Val Xgg
178. Xaa Val Xan Pro Pro Val Xgh
179. Xaa Val Xan Pro Pro Val Xgi
180. Xaa Val Xan Pro Pro Val Xgl
181. Xaa Val Xan Pro Pro Val Xgs
182. Xaa Val Xan Pro Pro Val Xgv
183. Xaa Val Xan Pro Pro Val Xhe
184. Xaa Val Xan Pro Pro Val Xgy
185. Xaa Val Xan Pro Pro Val Xhd
186. Xaa Val Xan Pro Pro Val Xhb
187. Xaa Val Xan Pro Pro Val Xhc
188. Xaa Val Xan Pro Pro Val Xhl
189. Xaa Val Xan Pro Pro Xeh
190. Xaa Val Xan Pro Pro Xen
191. Xaa Val Xan Pro Pro Xeo
192. Xaa Val Xan Pro Pro Xep
193. Xaa Val Xan Pro Pro Xeq
194. Xaa Val Xan Pro Pro Xer
195. Xaa Val Xan Pro Pro Xet
196. Xaa Val Xan Pro Pro Xeu
197. Xaa Val Xan Pro Pro Xes
198. Xaa Val Xan Pro Pro Xew
199. Xaa Val Xan Pro Pro Xez
200. Xaa Val Xan Pro Pro Xfc
201. Xaa Val Xan Pro Pro Xff
202. Xaa Val Xan Pro Pro Xfi
203. Xaa Val Xan Pro Pro Xfs
204. Xaa Val Xan Pro Pro Xfz
205. Xaa Val Xan Pro Pro Xgc
206. Xaa Val Xan Pro Pro Xgf
207. Xaa Val Xan Pro Pro Xgm
208. Xaa Val Xan Pro Pro Xgr
209. Xaa Val Xan Pro Pro Xgu
210. Xaa Val Xan Pro Pro Xgs
211. Xaa Val Xan Pro Pro Xgx
212. Xaa Val Xan Pro Pro Xha
213. Xaa Val Xan Pro Pro Xhk
214. Xaa Val Xan Pro Xek
215. Xaa Val Xan Pro Xen
216. Xaa Val Xan Pro Xer
217. Xaa Val Xan Pro Xep
218. Xaa Val Xan Pro Xeq
219. Xaa Val Xan Pro Xer
220. Xaa Val Xan Pro Xet

221. Xaa Val Xan Pro Xeu
222. Xaa Val Xan Pro Xes
223. Xaa Val Xan Pro Xfa
224. Xaa Val Xan Pro Xfd
225. Xaa Val Xan Pro Xfg
226. Xaa Val Xan Pro Xfl
227. Xaa Val Xan Pro Xfk
228. Xaa Val Xan Pro Xfm
229. Xaa Val Xan Pro Xfn
230. Xaa Val Xan Pro Xfo
231. Xaa Val Xan Pro Xfp
232. Xaa Val Xan Pro Xfq
233. Xaa Val Xan Pro Xfr
234. Xaa Val Xan Pro Xfy
235. Xaa Val Xan Pro Xgb
236. Xaa Val Xan Pro Xge
237. Xaa Val Xan Pro Xgk
238. Xaa Val Xan Pro Xgn
239. Xaa Val Xan Pro Xhi
240. Xaa Val Xan Pro Xgo
241. Xaa Val Xan Pro Xgp
242. Xaa Val Xan Pro Xgq
243. Xaa Val Xan Pro Xgt
244. Xaa Val Xan Pro Xgw
245. Xaa Val Xan Pro Xgz
246. Xaa Val Xan Pro Xhm
247. Xaa Xco Pro Pro Val Phe NH_2
248. Xaa Xcp Pro Pro Val Phe NH_2
249. Xaa Xcq Pro Pro Val Phe NH_2
250. Xaa Xcr Pro Pro Val Phe NH_2
251. Xaa Xcs Pro Pro Val Phe NH_2
252. Xaa Xct Pro Pro Val Phe NH_2
253. Xaa Xcu Pro Pro Val Phe NH_2
254. Xaa Xcw Pro Pro Val Phe NH_2
255. Xaa Xcv Pro Pro Val Phe NH_2
256. Xaa Xcx Pro Pro Val Phe NH_2
257. Xaa Xcy Pro Pro Val Phe NH_2
258. Xaa Xda Pro Pro Val Phe NH_2
259. Xaa Xdb Pro Pro Val Phe NH_2
260. Xaa Xdc Pro Pro Val Phe NH_2
261. Xaa Xdd Pro Pro Val Phe NH_2
262. Xaa Xdf Pro Pro Val Phe NH_2
263. Xaa Xdg Pro Pro Val Phe NH_2
264. Xaa Xdh Pro Pro Val Phe NH_2
265. Xaa Xco Pro Pro Val NH_2
266. Xaa Xcp Pro Pro Val NH_2
267. Xaa Xcq Pro Pro Val NH_2

268. Xaa Xcr Pro Pro Val NH_2
269. Xaa Xcs Pro Pro Val NH_2
270. Xaa Xct Pro Pro Val NH_2
271. Xaa Xcu Pro Pro Val NH_2
272. Xaa Xcw Pro Pro Val NH_2
273. Xaa Xcv Pro Pro Val NH_2
274. Xaa Xcx Pro Pro Val NH_2
275. Xaa Xcy Pro Pro Val NH_2
276. Xaa Xcz Pro Pro Val NH_2
277. Xaa Xda Pro Pro Val NH_2
278. Xaa Xdb Pro Pro Val NH_2
279. Xaa Xdc Pro Pro Val NH_2
280. Xaa Xde Pro Pro Val NH_2
281. Xaa Xdf Pro Pro Val NH_2
282. Xaa Xdg Pro Pro Val NH_2
283. Xaa Xdh Pro Pro Val NH_2
284. Xaa Xco Pro Pro NH_2
285. Xaa Xcp Pro Pro NH_2
286. Xaa Xcq Pro Pro NH_2
287. Xaa Xcr Pro Pro NH_2
288. Xaa Xcs Pro Pro NH_2
289. Xaa Xct Pro Pro NH_2
290. Xaa Xcu Pro Pro NH_2
291. Xaa Xcw Pro Pro NH_2
292. Xaa Xcv Pro Pro NH_2
293. Xaa Xcx Pro Pro NH_2
294. Xaa Xcy Pro Pro NH_2
295. Xaa Xcz Pro Pro NH_2
296. Xaa Xda Pro Pro NH_2
297. Xaa Xdb Pro Pro NH_2
298. Xaa Xdc Pro Pro NH_2
299. Xaa Xdd Pro Pro NH_2
300. Xaa Xdf Pro Pro NH_2
301. Xaa Xdg Pro Pro NH_2
302. Xaa Xdh Pro Pro NH_2
303. Xds Xan Pro Pro Val Phe NH_2
304. Xdt Xan Pro Pro Val Phe NH_2
305. Xdu Xan Pro Pro Val Phe NH_2
306. Xdv Xan Pro Pro Val Phe NH_2
307. Xdw Xan Pro Pro Val Phe NH_2
308. Xdx Xan Pro Pro Val Phe NH_2
309. Xdy Xan Pro Pro Val Phe NH_2
310. Xdz Xan Pro Pro Val Phe NH_2
311. Xea Xan Pro Pro Val Phe NH_2
312. Xeb Xan Pro Pro Val Phe NH_2
313. Xec Xan Pro Pro Val Phe NH_2
314. Xds Xan Pro Pro Val NH_2

315. Kdt Xan Pro Pro Val NH_2
316. Kdu Xan Pro Pro Val NH_2
317. Kdv Xan Pro Pro Val NH_2
318. Kdw Xan Pro Pro Val NH_2
319. Kdx Xan Pro Pro Val NH_2
320. Kdy Xan Pro Pro Val NH_2
321. Kdz Xan Pro Pro Val NH_2
322. Kea Xan Pro Pro Val NH_2
323. Keb Xan Pro Pro Val NH_2
324. Kec Xan Pro Pro Val NH_2
325. Kds Xan Pro Pro NH_2
326. Kdt Xan Pro Pro NH_2
327. Kdu Xan Pro Pro NH_2
328. Kdv Xan Pro Pro NH_2
329. Kdw Xan Pro Pro NH_2
330. Kdx Xan Pro Pro NH_2
331. Kdy Xan Pro Pro NH_2
332. Kdz Xan Pro Pro NH_2
333. Kea Xan Pro Pro NH_2
334. Keb Xan Pro Pro NH_2
335. Kec Xan Pro Pro NH_2
336. Kds Val Pro Pro Val Phe NH_2
337. Kds Val Pro Pro NH_2
338. Kdv Val Pro Pro NH_2
339. Kds Xan Pro Xfy
340. Kdv Xan Pro Xfy
341. Kaa Val Xhf Pro Pro Val Phe NH_2
342. Kaa Val Xhg Pro Pro Val Phe NH_2
343. Kaa Val Xhh Pro Pro Val Phe NH_2
344. Kaa Val Xhf Pro Pro Val NH_2
345. Kaa Val Xhg Pro Pro Val NH_2
346. Kaa Val Xhh Pro Pro Val NH_2
347. Kaa Val Xhf Pro Pro NH_2
348. Kaa Val Xhg Pro Pro NH_2
349. Kaa Val Xhh Pro Pro NH_2
350. Kaa Val Xhf Pro Xfy
351. Kaa Val Xhg Pro Xfy
352. Kaa Val Xhh Pro Xfy
353. Kaa Val Xhf Pro Xgb
354. Kaa Val Xhg Pro Xgb
355. Kaa Val Xhh Pro Xgb
356. Ked Val Xan Pro Xfy
357. Kby Val Xan Pro Xfy
358. Kby Val Xan Pro Xhi
359. Kef Val Xan Pro Xfy
360. Kef Val Xan Pro Xhi
361. Kca Val Xan Pro Xfy

362. Xca Val Xan Pro Xhi
363. Xaa Val Xan Pro Xdp Phe NH_2
364. Xaa Val Xan Pro Xdq Phe NH_2
365. Xaa Val Xan Pro Xdr Phe NH_2
366. Xaa Val Xan Pro Xdp NH_2
367. Xaa Val Xan Pro Xdq NH_2
368. Xaa Val Xan Pro Xdr NH_2
369. Xaa Val Xan Pro Pro Xdi NH_2
370. Xaa Val Xan Pro Pro Xcs NH_2
371. Xaa Val Xan Pro Pro Xct NH_2
372. Xaa Val Xan Pro Pro Xcu NH_2
373. Xaa Xcs Pro Pro Xdi NH_2
374. Xaa Xct Pro Pro Xdi NH_2
375. Xaa Xcs Pro Xdp Phe NH_2
376. Xaa Xct Pro Xdp Phe NH_2
377. Xaa Xcs Pro Xdp NH_2
378. Xaa Xct Pro Xdp NH_2
379. Xaa Xcs Pro Xdq NH_2
380. Xaa Xct Pro Xdq NH_2
381. Xaa Xcs Pro Xdr NH_2
382. Xaa Xct Pro Xdr NH_2
383. Xaa Val Xan Pro Pro Xdi NH_2
384. Xaa Val Xan Pro Pro Xdk NH_2
385. Xaa Val Xan Pro Pro Xdl NH_2
386. Xaa Val Xan Pro Pro Xdm NH_2
387. Xaa Val Xan Pro Pro Xdn NH_2
388. Xaa Val Xan Pro Pro Xdo NH_2
389. Xca Val Xan Pro Pro Phe Phe NH_2
390. Xby Val Xan Pro Pro Phe Phe NH_2
391. Xca Val Xan Pro Pro Phe Phe NH_2
392. Xef Val Xhf Pro Pro tLeu Phe NH_2
393. Xef Val Xhf Pro Pro tLeu Aic NH_2
394. Xef Val Xhf Pro Pro tLeu Tic NH_2
395. Xef Val Xan Pro Xfy
396. Xef Val Xan Pro Xbg
397. Xef Val Xan Pro Xbh
398. Xef Val Xan Pro Xgn
399. Xca Xct Pro Xfy
400. Xaa tLeu Xan Pro Pro Val Phe NH_2
401. Xaa Leu Xan Pro Pro Val Phe NH_2
402. Xaa Ile Xan Pro Pro Val Phe NH_2
403. Xaa Val Xan Pro Pro tLeu Phe NH_2
404. Xaa Val Xan Pro Pro Leu Phe NH_2
405. Xaa Val Xan Pro Pro Ile Phe NH_2
406. Xaa Val Xan Pro Pro Val Dab NH_2
407. Xaa Val Xan Pro Pro Val Ala NH_2
408. Xaa Dab Xan Pro Pro Val Phe NH_2

409. Xaa Dab Xan Pro Pro Val NH_2
410. Xaa Dab Xan Pro Pro NH_2
411. Xht Val Xan Pro Pro Val Phe NH_2
412. Xhu Val Xan Pro Pro Val Phe NH_2
413. Xht Val Xan Pro Pro Val NH_2
413(a). Xhu Val Xan Pro Pro Val NH_2
414. Xht Val Xan Pro Pro NH_2
415. Xhu Val Xan Pro Pro NH_2
416. Xaa Val Xhy Pro Pro Val Phe NH_2
417. Xaa Val Xhz Pro Pro Val Phe NH_2
418. Xaa Val Xhy Pro Pro Val NH_2
419. Xaa Val Xhz Pro Pro Val NH_2
420. Xaa Val Xhy Pro Pro NH_2
421. Xaa Leu Xhz Pro Pro NH_2
422. Xaa Val Xhy Xfy
423. Xa Val Xhz Xfy
424. Xhv Val Xan Pro Pro Val Phe NH_2
425. Xhw Val Xan Pro Pro Val Phe NH_2
426. Xhx Val Xan Pro Pro Val Phe NH_2
427. Xhv Val Xan Pro Pro Val NH_2
428. Xhw Val Xan Pro Pro Val NH_2
429. Xhx Val Xan Pro Pro Val NH_2
430. Xhv Val Xan Pro Pro NH_2
431. Xhw Val Xan Pro Pro NH_2
432. Xhx Val Xan Pro Pro NH_2
433. Xaa Val Xan Pro Xia
434. Xaa Val Xan Pro Xib
435. Xaa Val Xan Pro Xic
436. Xaa Val Xan Pro Xid
437. Xaa Val Xan Pro Xie
438. Xby Val Xan Pro Xia
439. Xby Val Xan Pro Xib
440. Xby Val Xan Pro Xic
441. Xby Val Xan Pro Xid
442. Xby Val Xan Pro Xie
443. Xca Val Xan Pro Xia
444. Xca Val Xan Pro Xib
445. Xca Val Xan Pro Xic
446. Xca Val Xan Pro Xid
447. Xca Val Xan Pro Xie
448. Xed Val Xan Pro Xia
449. Xed Val Xan Pro Xib
450. Xed Val Xan Pro Xic
451. Xed Val Xan Pro Xid
452. Xed Val Xan Pro Xie
453. Xby Leu Xan Pro Xia
454. Xby Leu Xan Pro Xib

455. Xby Ile Xan Pro Xic
456. Xby Ile Xan Pro Xid
457. Xby Leu Xan Pro Xie
458. Xca Leu Xan Pro Xia
459. Xca Val Xao Pro Xib
460. Xca Val Xao Pro Xic
461. Xat Val Xhf Pro Xak Leu Phe NH_2
462. Xat Val Xhf Pro Xhr Leu Phe NH_2
463. Xed Val Xhf Pro Xak Leu Phe NH_2
464. Xed Val Xhf Pro Xhr Leu Phe NH_2
465. Xat Val Xhf Pro Xak Val NH_2
466. Xat Val Xhf Pro Xhr Val NH_2
467. Xed Val Xhf Pro Xak Val NH_2
468. Xed Val Xhf Pro Xhr Val NH_2
469. Xat Val Xhf Pro Xak NH_2
470. Xat Val Xhf Pro Xhr NH_2
471. Xed Val Xhf Pro Xak NH_2
472. Xat Val Xhf Pro Xia
473. Xat Val Xhf Pro Xib
474. Xed Val Xhf Pro Xic
475. Xed Val Xhf Pro Xid
476. Xat Val Xhf Pro Xie
477. Xat Val Xhf Pro Xhs NH_2
478. Xed Val Xhf Pro Xhs NH_2
479. Xat Val Xhf Pro Xak Xfz
480. Xat Val Xhf Pro Xhr Xfz
481. Xed Val Xhf Pro Xak Xfz
482. Xed Val Xhf Pro Xhr Xfz
483. Xat Val Xhf Pro Xak Xbw
484. Xat Val Xhf Pro Xhr Xbw
485. Xed Val Xhf Pro Xak Xbw
486. Xed Val Xhf Pro Xhr Xbw
487. Xat Val Xhf Pro Xak Xer
488. Xat Val Xhf Pro Xhr Xer
489. Xed Val Xhf Pro Xak Xer
490. Xed Val Xhf Pro Xhr Xer
491. Xat Val Xhf Pro Xak Xgi
492. Xat Val Xhf Pro Xhr Xgi
493. Xed Val Xhf Pro Xak Xgi
494. Xed Val Xhf Pro Xhr Xgi
495. Xat Val Xhf Pro Xak Xif
496. Xat Val Xhf Pro Xhr Xif
497. Xed Val Xhf Pro Xak Xif
498. Xed Val Xhf Pro Xhr Xif
499. Xat Val Xhf Pro Xak Xig
500. Xat Val Xhf Pro Xhr Xig
501. Xed Val Xhf Pro Xak Xig

502. Xed Val Khf Pro Khr Xig
503. Xaa Val Xan Pro Pro Xif
504. Xaa Val Xan Pro Xig
505. Xca Val Xan Pro Pro Xif
506. Xca Val Xan Pro Xig
507. Xby Val Xan Pro Pro Xif
508. Xby Val Xan Pro Xig
509. Xed Val Xan Pro Pro Xif
510. Xed Val Xan Pro Xig
511. Xaa Leu Xan Pro Pro Xif
512. Xaa Leu Xan Pro Xig
513. Xca Leu Xan Pro Pro Xif
514. Xca Leu Xan Pro Xig
515. Xby Leu Xan Pro Pro Xif
516. Xby Leu Xan Pro Xig
517. Xed Leu Xan Pro Pro Xif
518. Xed Leu Xan Pro Xig
519. Xaa Lys Xan Pro Pro Val Phe NH_2
520. Xaa Lys Xan Pro Pro Val NH_2
521. Xaa Lys Xan Pro Pro NH_2
522. Xaa Lys Xan Pro Xfy
523. Xaa Chg Xan Pro Pro Val NH_2
524. Xaa Chg Xan Pro Pro NH_2
525. Xaa Chg Xan Pro Pro Val Phe NH_2
526. Xaa Val Xii Pro Pro Val Phe NH_2
527. Xaa Val Xii Pro Pro Val NH_2
528. Xaa Val Xii Pro Pro NH_2
529. Xaa Val Xan Pro Pro Val Lys NH_2
530. Xaa Val Xan Pro Xik
531. Xaa Val Xan Pro Pro Xil NH_2
532. Xaa Val Xbu
533. Xby Val Xbu
534. Xca Val Xbu
535. Xaa Val Xbv
536. Xby Val Xbv
537. Xca Val Xbv
538. Xaa Val Xan Pro Pro Xab
539. Xaa Val Xan Xab
540. Xim Val Xan Pro Pro Val Phe NH_2
541. Xin Val Xan Pro Pro Val Phe NH_2
542. Xio Val Xan Pro Pro Val Phe NH_2
543. Xip Val Xan Pro Pro Val Phe NH_2
544. Xiq Val Xan Pro Pro Val Phe NH_2
545. Xkd Val Xan Pro Pro Val Phe NH_2
546. Xim Val Xan Pro Pro Val NH_2
547. Xin Val Xan Pro Pro Val NH_2
548. Xio Val Xan Pro Pro Val NH_2

549. Xip Val Xan Pro Pro Val NH_2
550. Xiq Val Xan Pro Pro Val NH_2
551. Xkd Val Xan Pro Pro Val NH_2
552. Xim Val Xan Pro Pro NH_2
553. Xin Val Xan Pro Pro NH_2
554. Xio Val Xan Pro Pro NH_2
555. Xip Val Xan Pro Pro NH_2
556. Xiq Val Xan Pro Pro NH_2
557. Xkd Val Xan Pro Pro NH_2
558. Xaa Val Xan Pro Pro Val Xir
559. Xaa Val Xan Pro Pro Val Xis
560. Xaa Val Xan Pro Pro Val Xit
561. Xaa Val Xan Pro Pro Val Xiu
562. Xaa Val Xan Pro Pro Xiv
563. Xaa Val Xan Pro Pro Xiw
564. Xaa Val Xan Pro Pro Xiy
565. Xaa Val Xan Pro Pro Xix
566. Xaa Val Xan Pro Xiz
567. Xaa Val Xan Pro Xka
568. Xaa Val Xan Pro Xkb
569. Xaa Val Xan Pro Xkc
570. Xke Val Xan Pro Pro Val Phe NH_2
571. Xkf Val Xan Pro Pro Val Phe NH_2
572. Xkg Val Xan Pro Pro Val Phe NH_2
573. Xkh Val Xan Pro Pro Val Phe NH_2
574. Xke Val Xan Pro Pro Val NH_2
575. Xkf Val Xan Pro Pro Val NH_2
576. Xkg Val Xan Pro Pro Val NH_2
577. Xkh Val Xan Pro Pro Val NH_2
578. Xke Val Xan Pro Pro NH_2
579. Xkf Val Xan Pro Pro NH_2
580. Xkg Val Xan Pro Pro NH_2
581. Xkh Val Xan Pro Pro NH_2
582. Xaa Xcz Pro Pro Val Phe NH_2
583. Xed Val Xhf Pro Xhr NH_2

Examples for the MS-characterization of the synthesized novel compounds are given in the following table.

EXAMPLE No.	Fast atom bombardment. M S analysis Mol.-Weight (measured)	EXAMPLE No.	Fast atom bombardment M S analysis Mol.-Weight (measured)
3	798	56	550
16	810	101	853
24	811	115	845
28	811	139	579
30	825	234	641
33	881	403	811
34	845	544	869
37	649		

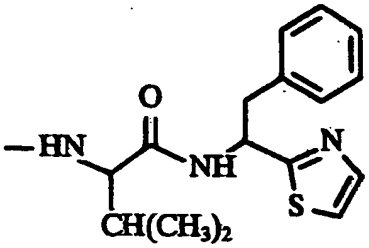
Table I - Sequence Identification of Compounds Prepared According to Examples 1 and 2

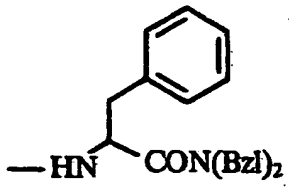
Compound Number(s)	Sequence ID Number
38, 39, 52, 86-91, 93, 214-246, 350-362, 366-368, 395-398, 433-452, 459, 460, 469-478, 504, 506, 508, 510, 530, 566-569, 583	2
3, 9, 26-28, 30-33, 35, 36, 95-117, 341-343, 416, 417, 424-426, 526, 540-545, 570-573	3
4-7, 10, 11, 406, 558-561	4
8	5
12	6
13, 392, 403	7
14	8
15, 16, 29	9
17, 18	10
19, 20	11
21, 22, 247-264, 303-313, 582	12
23, 402	13
24, 400	14
25, 401	15
34	16
37, 118-138, 344-346	17
40, 45, 189-213, 369-372, 383-388, 503, 505, 507, 509, 531, 538, 562-565	18
41-43, 48, 49, 527	19
44	20
46, 50, 51, 62-65, 70, 139-159, 347-349, 414, 415, 420, 421, 430-432, 528, 552-557, 578-581	21
47	22
53-61, 78, 422, 423, 539	23
66, 67, 94, 410, 524	24
68, 69, 284-302, 325-335	25

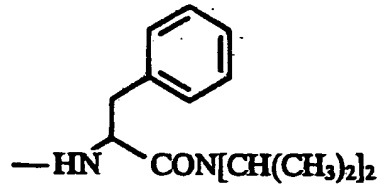
Compound Number(s)	Sequence ID Number
73, 83-85	26
92	27
160-188	28
265-283, 314-324	29
336	30
337, 338	31
339, 340, 377-382, 399	32
363-365	33
373, 374	34
375, 376	35
389-391	36
393, 394	37
404	38
405	39
407	40
408	41
409	42
411, 412, 418, 419, 427-429, 546-551, 574-577	43
413, 413(a), 453, 454, 457, 458, 512, 514, 516, 518	44
455, 456	45
465-468	46
461-464	47
479-502	48
515, 517	49
513	50
519	51
520	52
521	53
522	54
523	55
525	56
529	57

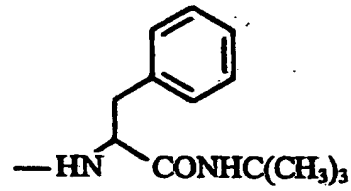
The symbols Xaa... in the summary have the following meanings:

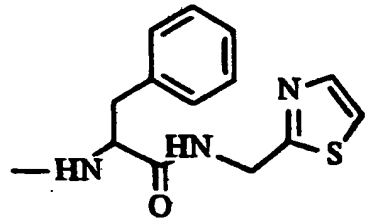
Xaa: N,N-Dimethylvaline

Xab: 

Xac: 

Xad: 

Xae: 

Xaf: 

Xag: Tetrahydroisoquinoline carboxylic acid

Xah: 1-Aminoindane-1-carboxylic acid

Xai: tert-Leucine or 2-tert-butylglycine

Xak: Homoproline or pipecolic acid

Xal: 1-aminopentane-1-carboxylic acid

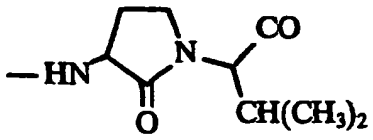
Xam: N-Methylisoleucine

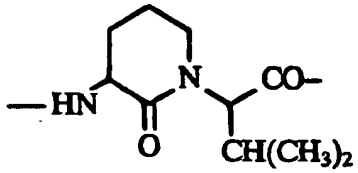
Xan: N-Methylvaline

Xao: N-Methylleucine

Xan: N-Methylvaline

Xao: N-Methylleucine

Xap: 

Xaq: 

Xar: N-N-Dimethylisoleucine

Xas: N,N-Dimethylleucine

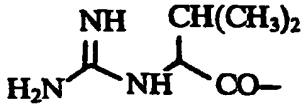
Xat: N,N-Dimethyl-tert-leucine

Xau: N,N-Dimethyl-3-tert-butylalanin

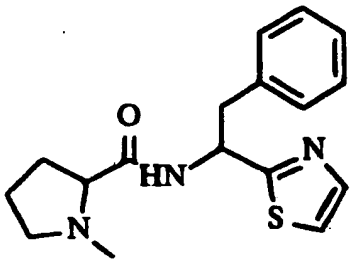
Xav: N-Acetyl-N-methylvaline

Xaw: N-Methyl-N-benzylvaline

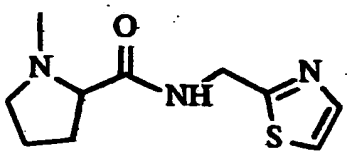
Xax: N,N-Dibutylvaline

Xaz: 

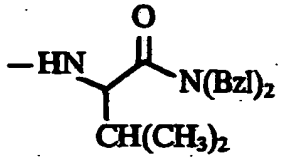
Xba: N-Benzylvaline

Xbb: 

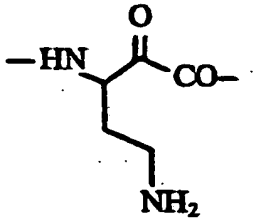
Xbc:



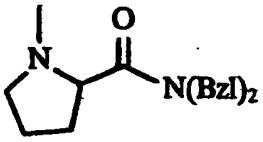
Xbd:



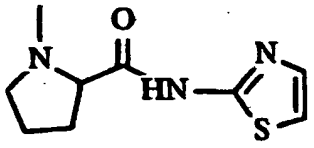
Xbe:



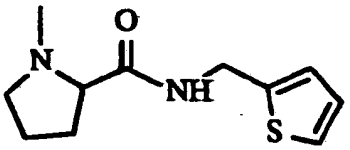
Xbf:



Xbg:



Xbh:



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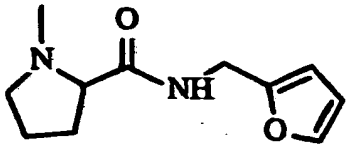

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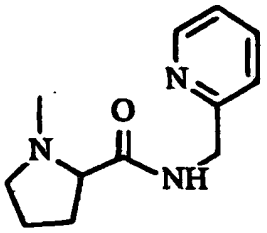
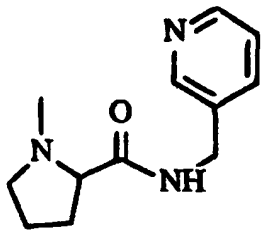
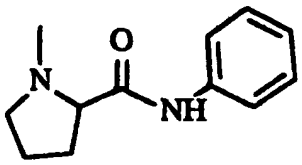
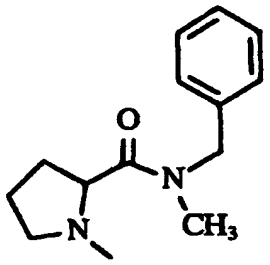


Xbl: 

Xbm: 

Xbn: 

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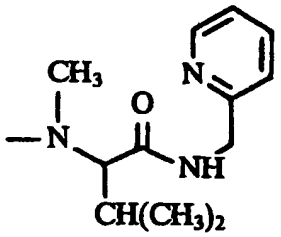
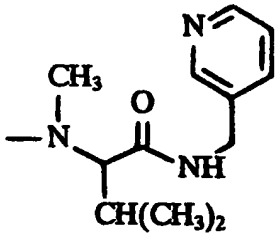
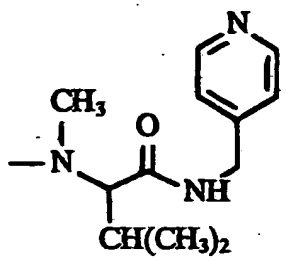
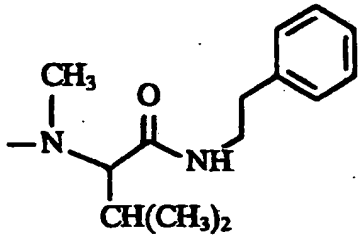
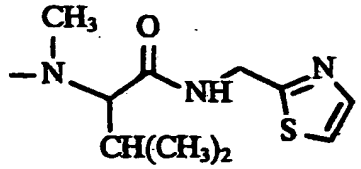
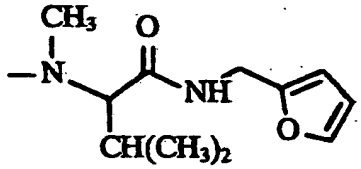
Xbp: 

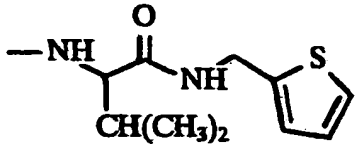
Xbq: 

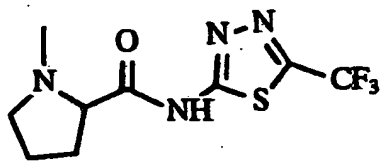
Xbr: 

Xbt: 

Xbu: 

Xbv: 

Xbw: 

Xbx: 

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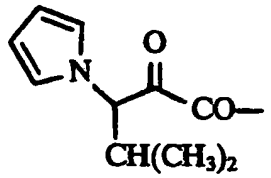
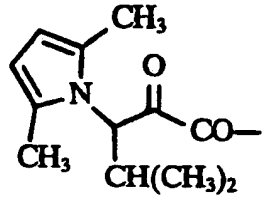
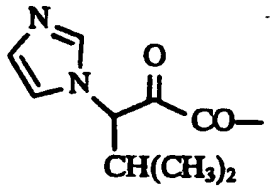
Xbz: N,N−Bis(2−fluoroethyl)valine

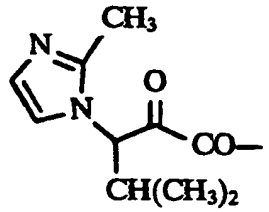
Xca:N,N−Dipropylvaline

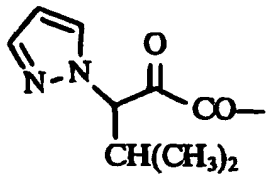
Xcb: N−Cyclopropylvaline

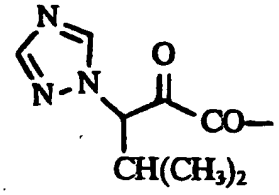
Xcc: 

Xcd: 

Xce: 

Xcf: 

Xcg: 

Xch: 

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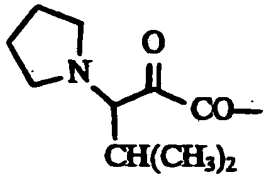

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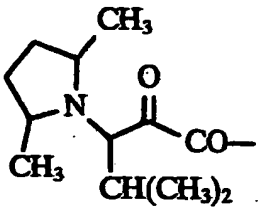

Xcl:

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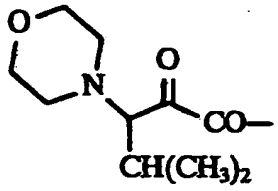

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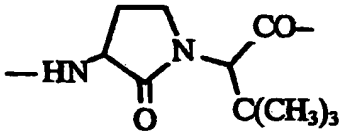

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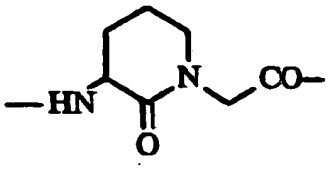
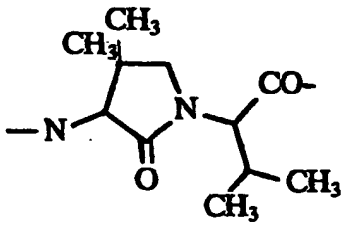
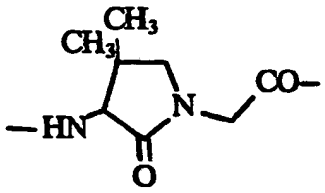
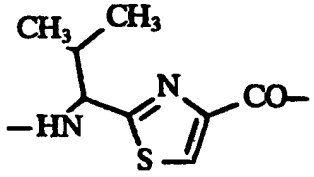
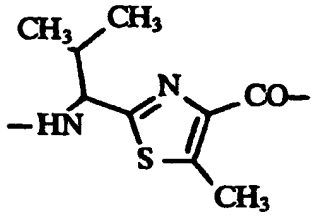
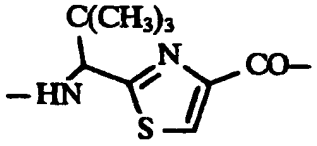


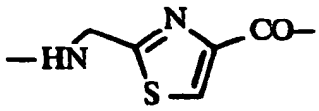
Xcq: 

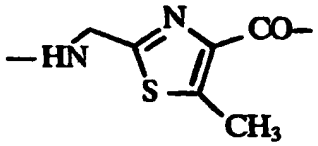
Xcr: 

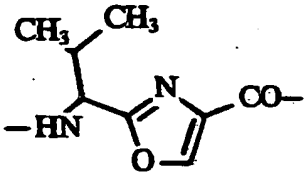
Xcs: 

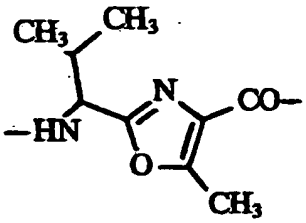
Xct: 

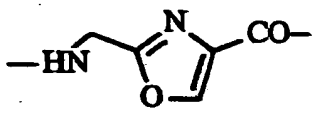
Xcu: 

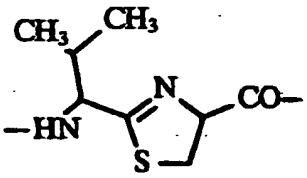
Xcv: 

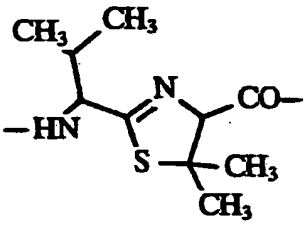
Xcw: 

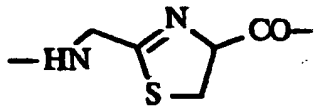
Xcx: 

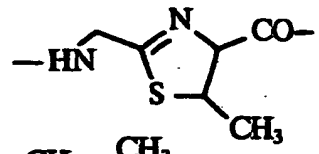
Xcy: 

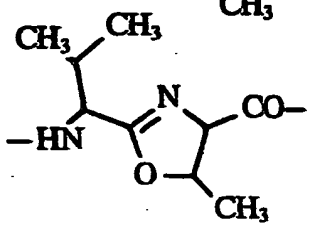
Xcz: 

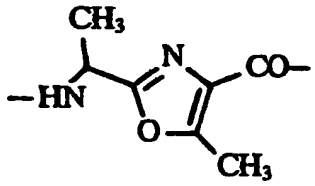
Xda: 

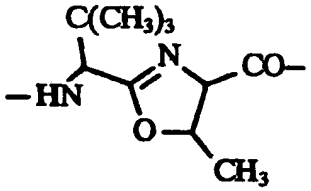
Xdb: 

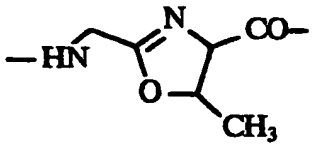
Xdc: 

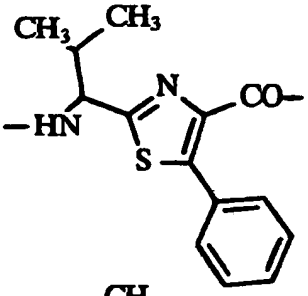
Xdd: 

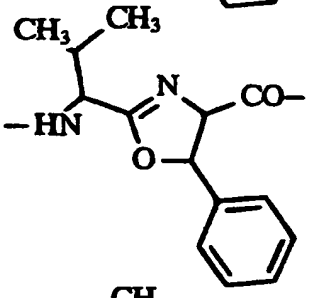
Xde: 

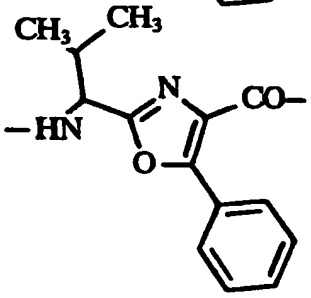
Xdf: 

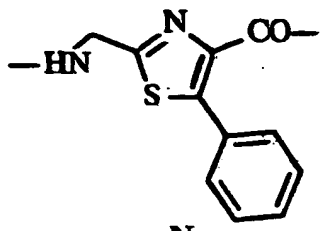
Xdg: 

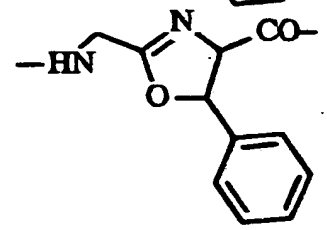
Xdh: 

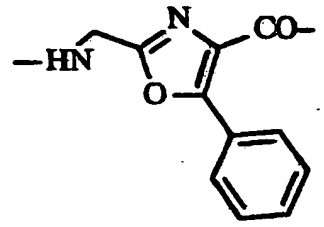
Xdi: 

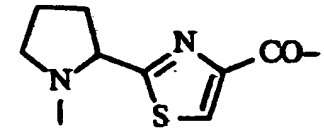
Xdk: 

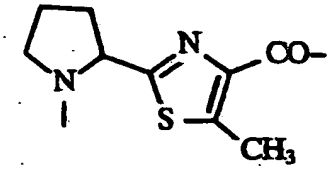
Xdl: 

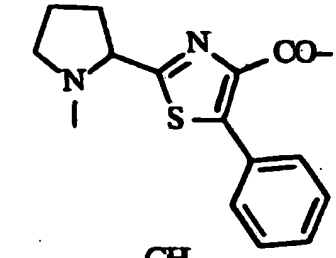
Xdm: 

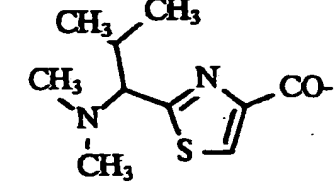
Xdn: 

Xdo: 

Xdp: 

Xdq: 

Xdr: 

Xds: 

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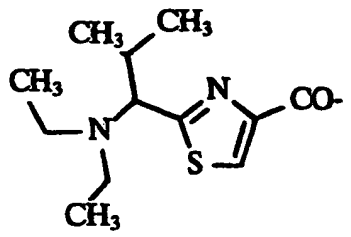

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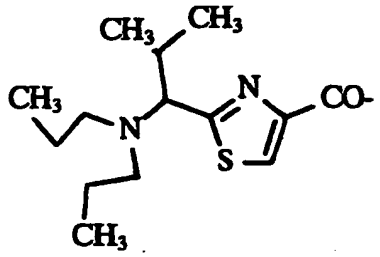

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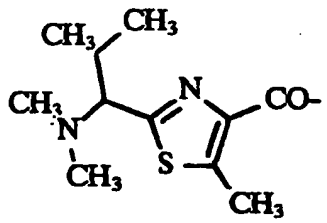

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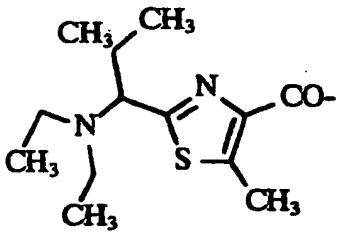

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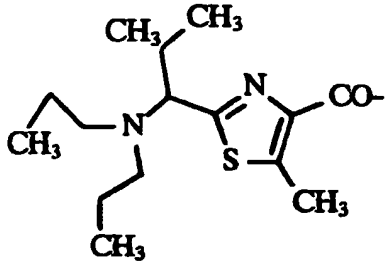

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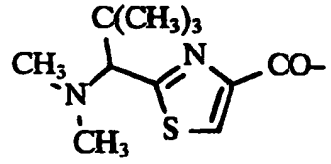
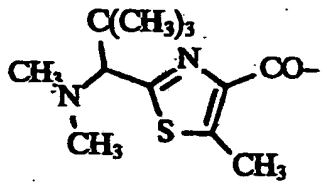
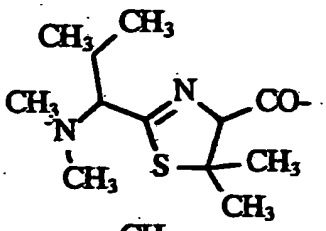
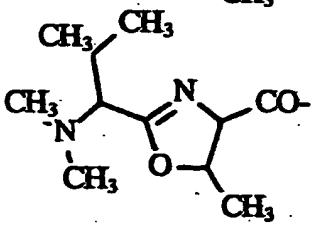
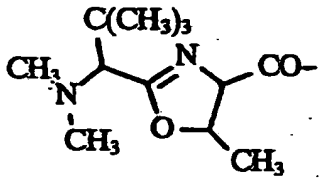


Xdz: 

Xea: 

Xeb: 

Xec: 

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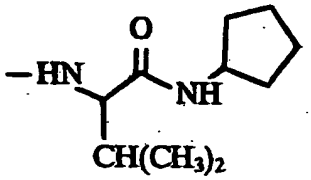
Xeh: 

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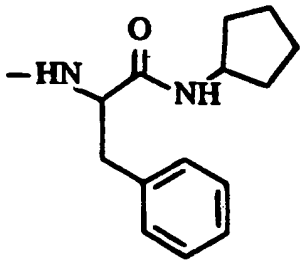

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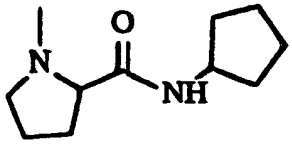

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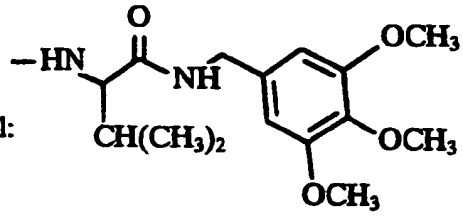

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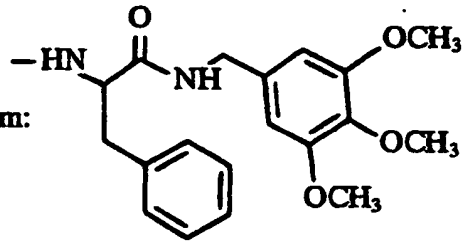

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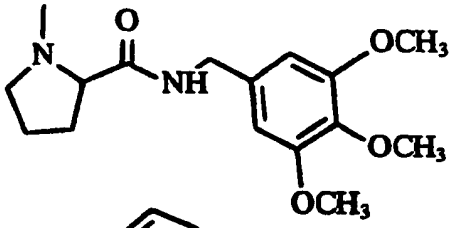

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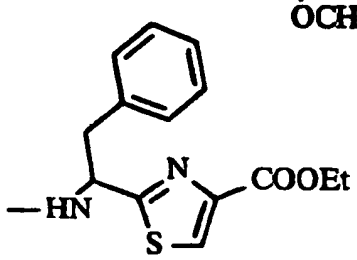
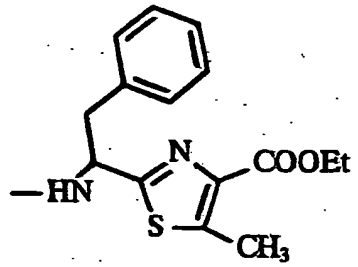
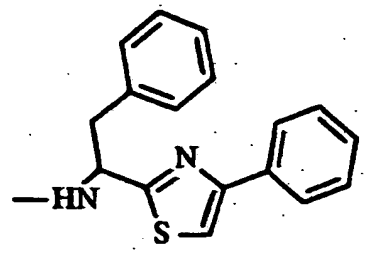
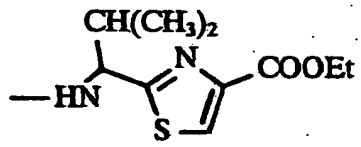
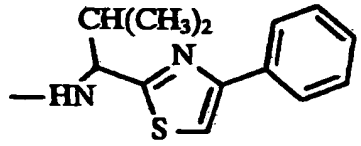
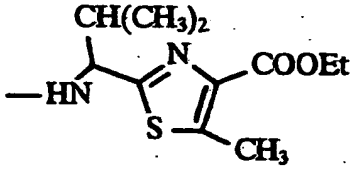


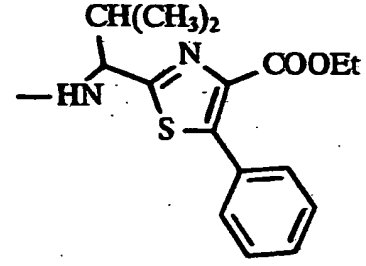
Xep: 

Xeq: 

Xer: 

Xes: 

Xet: 

Xeu: 

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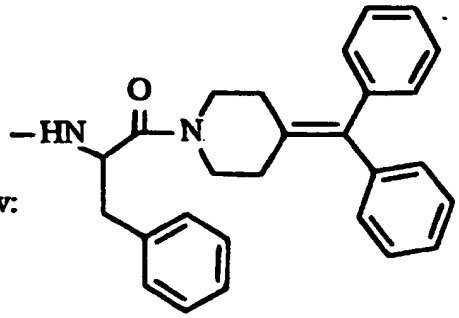

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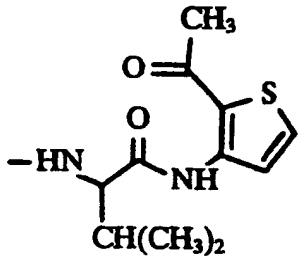

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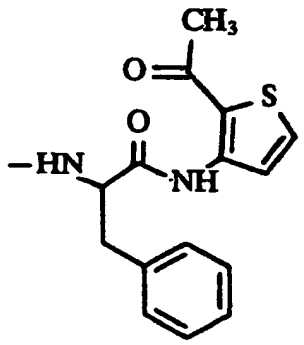

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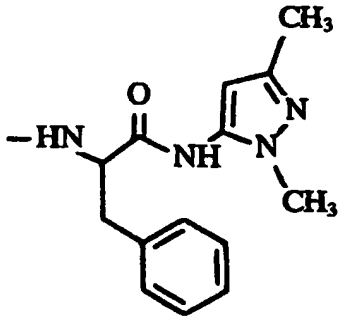
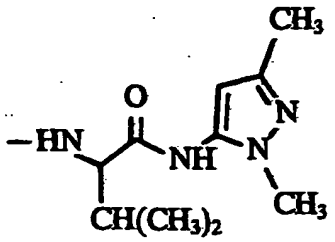
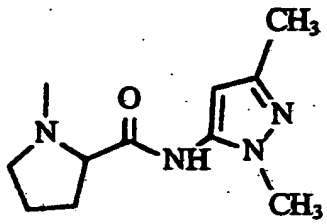
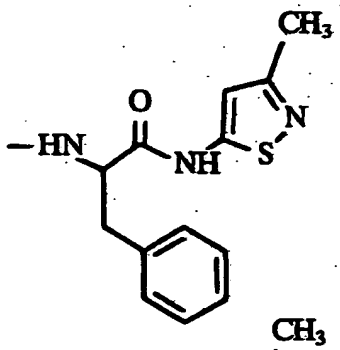
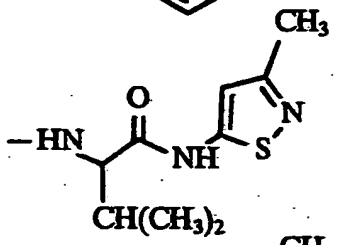
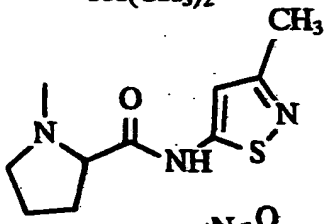


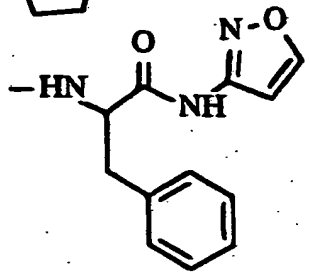
Xez: 

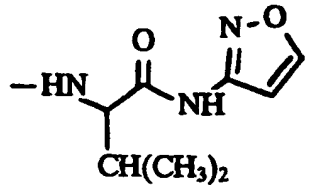
Xfa: 

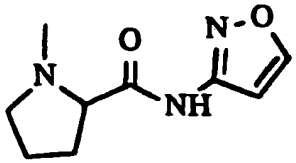
Xfb: 

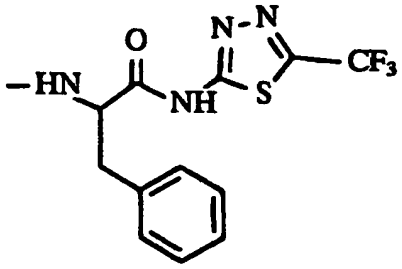
Xfc: 

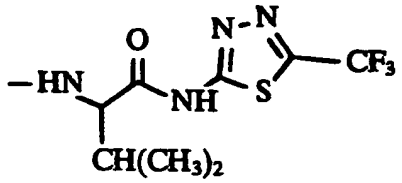
Xfd: 

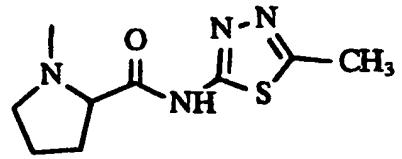
Xfe: 

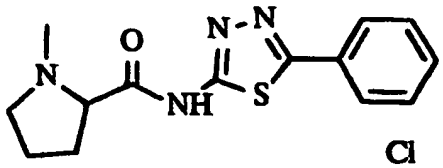
Xff: 

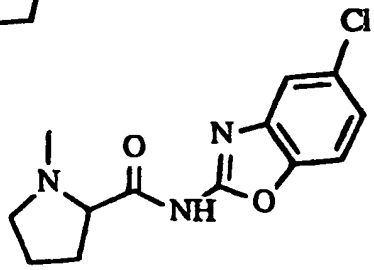
Xfg: 

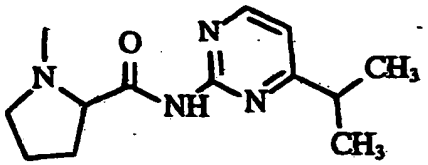
Xfh: 

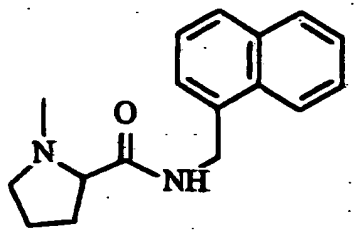
Xfi: 

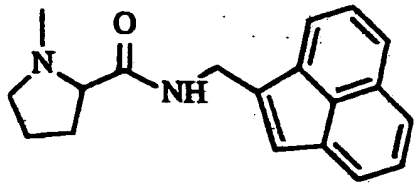
Xfk: 

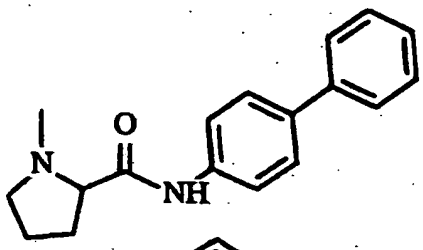
Xfl: 

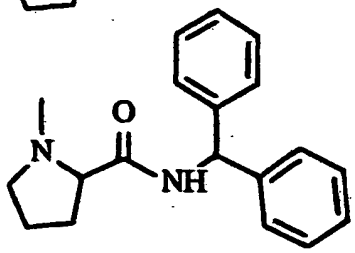
Xfm: 

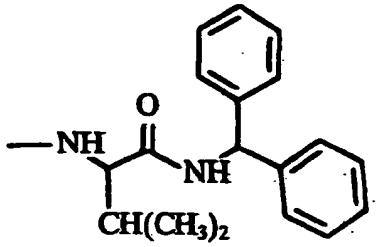
Xfn: 

Xfo: 

Xfp: 

Xfq: 

Xfr: 

Xfs: 

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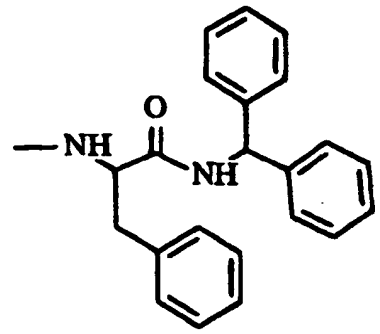

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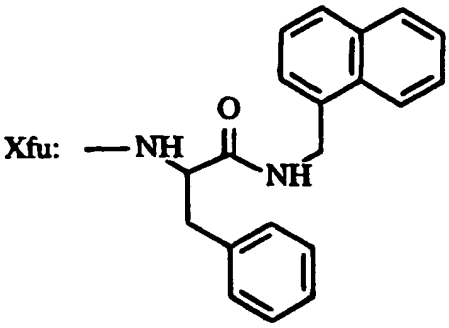

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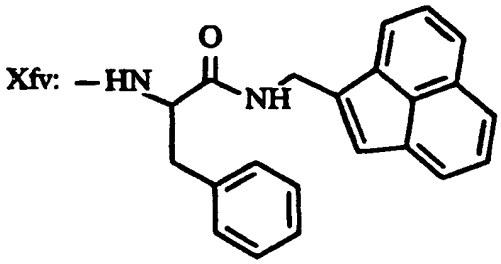

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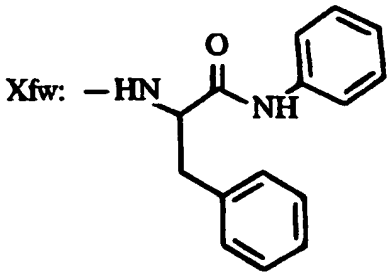

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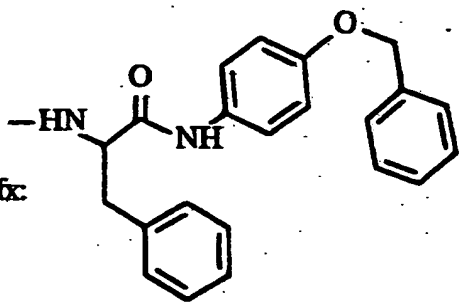

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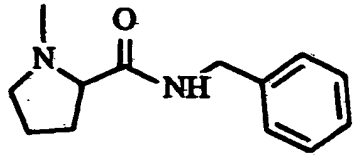

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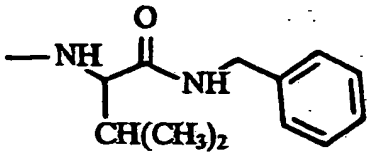

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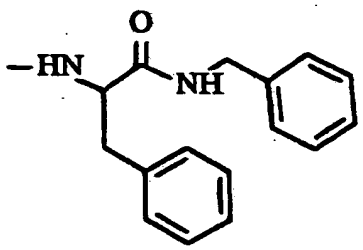

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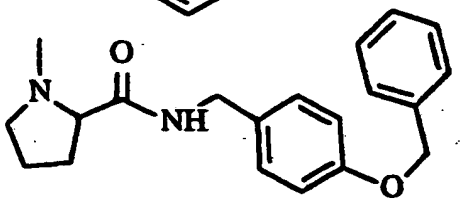

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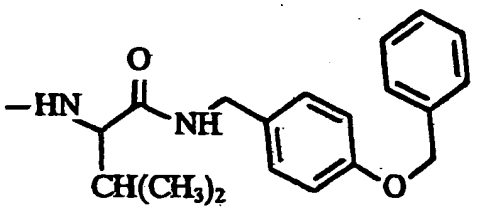

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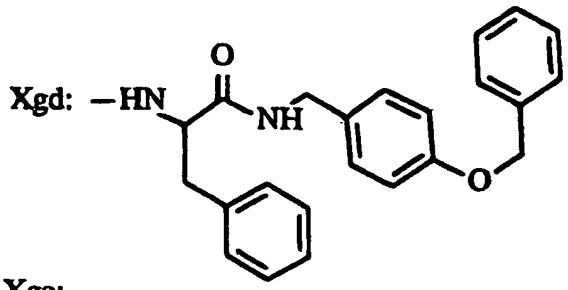

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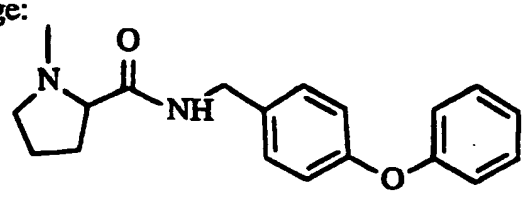

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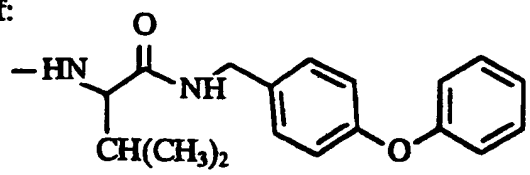

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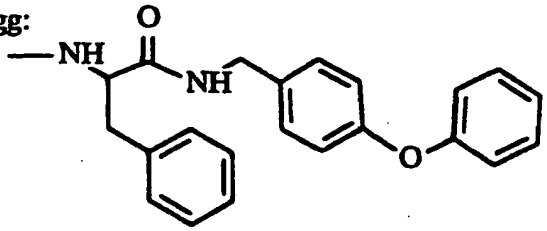

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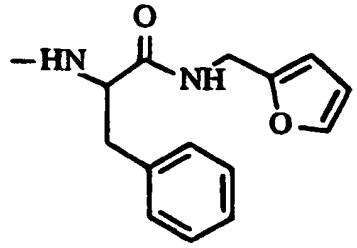

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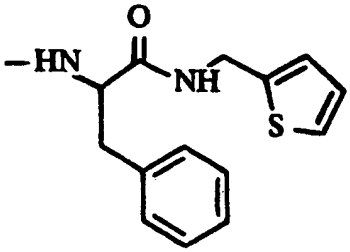

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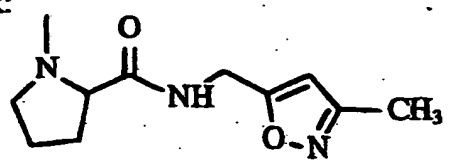

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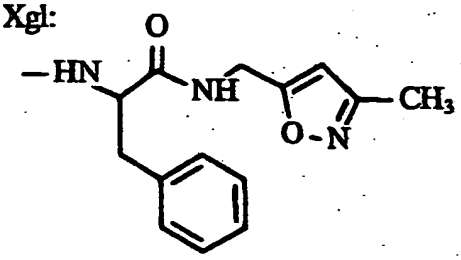

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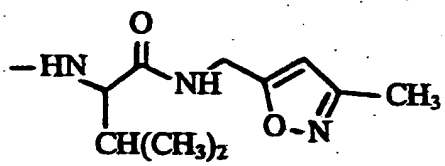

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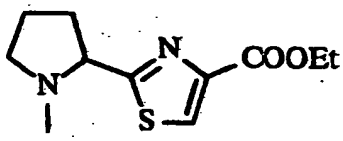

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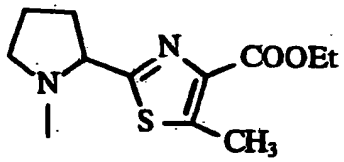

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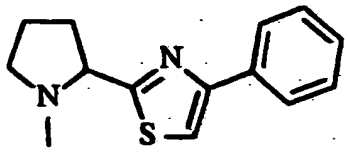

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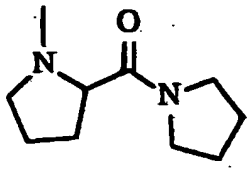

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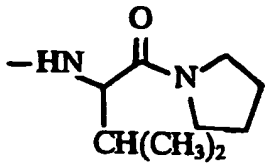

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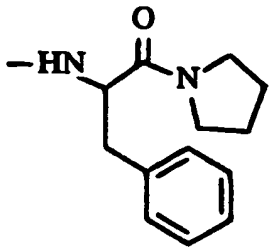

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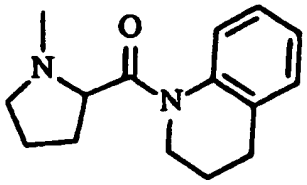

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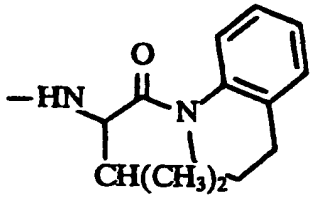

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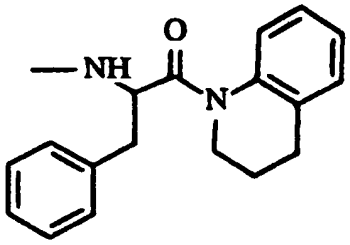

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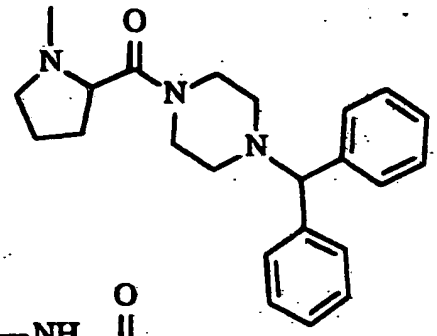

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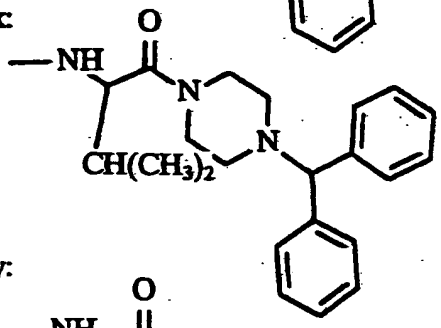

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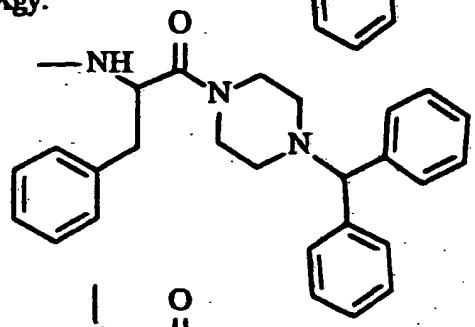

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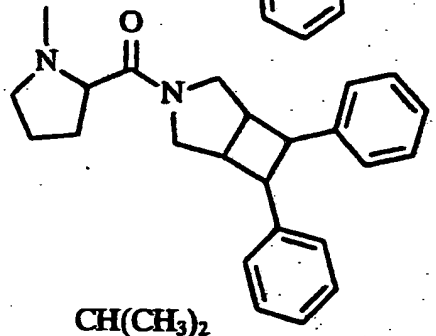

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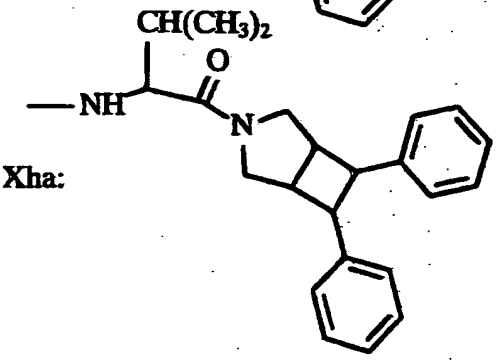
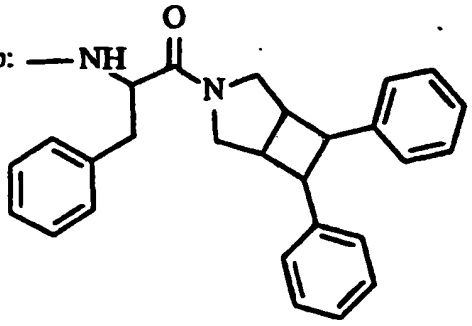
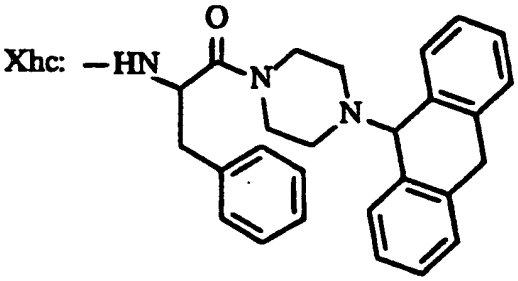
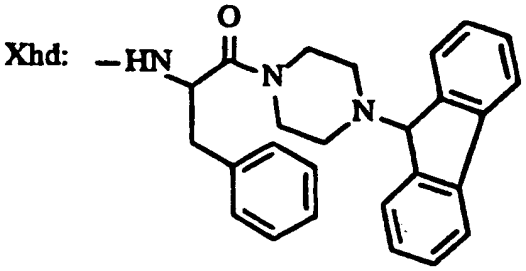
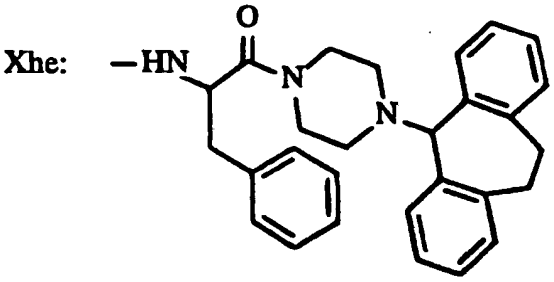


Xhb: 

Xhc: 

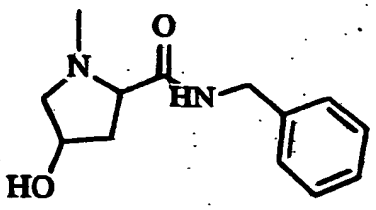
Xhd: 

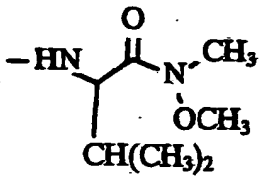
Xhe: 

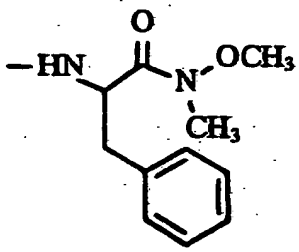
Xhf: N-Methyl-2-tert-butylglycine

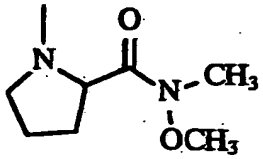
Xhg: N-Methyl-3-tert-butylalanine

Xhh: N-Ethylvaline

Xhi: 

Xhk: 

Xhl: 

Xhm: 

Xhn: N–Ureyl–valine

Xho: N,N–Dimethylphenylalanine

Xhp: N,N–Diethylphenylalanine

Xhq: N,N–Dipropylphenylalanine

Xhr: Hydroxyproline

Xhs: 3–Thienylalanine

Xht: N,N–Dimethyl–3–cyclohexyl–alanine

Xhu: N,N–Diethyl–3–cyclohexyl–alanine

Xhv: N-Methyl-N-isopropyl-tert.-leucine

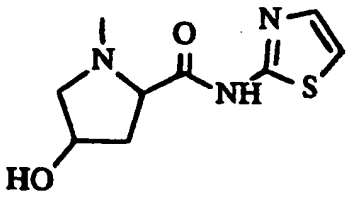
Xhw: N-Methyl-N-isopropyl-leucine

Xhx: N-Methyl-N-isopropyl-isoleucine

Xhy: N-Methyl-3-cyclohexyl-alanine

Xhz: N-Methyl-phenylalanine

Xia:



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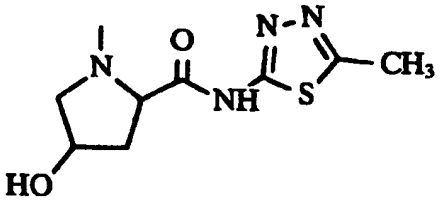

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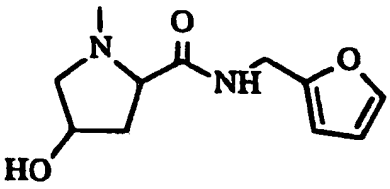

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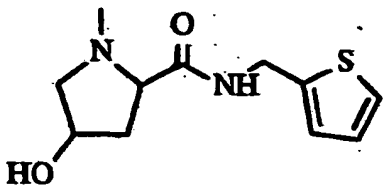

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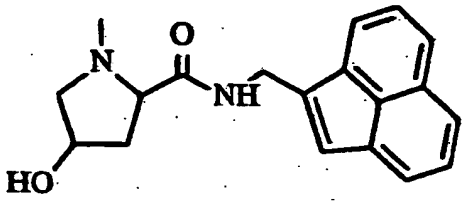

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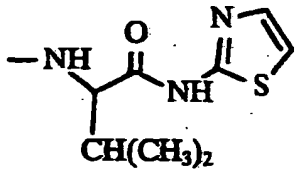

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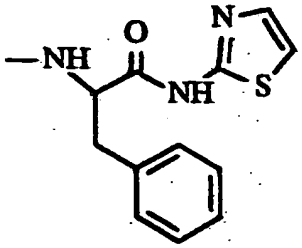
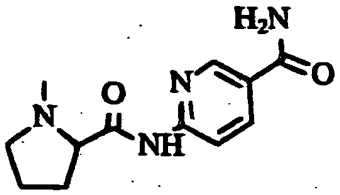
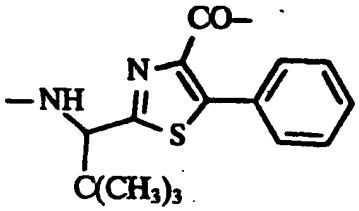


Xih: 2–Cyclohexylglycine

Xii: N–Methyl–2–cyclohexylglycine

Xik:



Xil: 

Xim: N–Methylaminosulfonyl–valine

Xin: N–tert.butylaminosulfonyl–valine

Xio: N–Morpholinosulfonyl–valine

Xip: N–Benzyloxycarbonyl–valine

Xiq: N–tert.Butyloxycarbonyl–valine

Xir: Phenylalanine–methylester

Xis: Phenylalanine–ethylester

Xit: Phenylalanine–benzylester

Xiu: Phenylalanine–tert.butylester

Xiv: Valine–benzylester

Xiw: Valine–methylester

Xix: Valine–ethylester

Xiy: Valine–tert.butylester

Xiz: Proline–benzylester

Xka: Proline–methylester

Xkb: Proline–ethylester

Xkc: Proline–tert.butylester

Xkd: N–Lactyl–valine

Xke: N–Methylsulfonyl–valine

Xkf: N–Methyl–N–methylsulfonyl–valine

Xkg: N–Tosyl–valine

Xkh: N–Phthalyl–valine

The ending $-NH_2$ has the meaning that the C-terminal amino acid is in its amide form.

Compounds of this invention may be assayed for anti-cancer activity by conventional methods, including for example, the methods described below.

A. In vitro methodology

Cytotoxicity may be measured using a standard methodology for adherent cell lines such as the microculture tetrazolium assay (MTT). Details of this assay have been published (Alley, MC et al, Cancer Research 48:589-601, 1988). Exponentially growing cultures of tumor cells such as the HT-29 colon carcinoma or LX-1 lung tumor are used to make microtiter plate cultures. Cells are seeded at 5000-20,000 cells per well in 96-well plates (in 150 µl of media), and grown overnight at 37°C. Test compounds are added, in 10-fold dilutions varying from 10^{-4} M to 10^{-10} M. Cells are then incubated for 48 hours. To determine the number of viable cells in each well, the MTT dye is added (50 µl of 3 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide in saline). This mixture is incubated at 37°C for 5 hours, and then 50 µl of 25 % SDS, pH2 is added to each well. After an overnight incubation, the absorbance of each well at 550 nm is read using an ELISA reader. The values for the mean +/- SD of data from replicated wells are calculated, using the formula % T/C (% viable cells treated/control).

$$\frac{\text{OD of treated cells}}{\text{OD of control cells}} \times 100 = \% \text{ T/C}$$

The concentration of test compound which gives a T/C of 50 % growth inhibition was designated as the IC_{50}.

B. In vivo methodology

Compounds of this invention may be further tested in any of the various pre-clinical assays for in vivo activity which are indicative of clinical utility. Such assays are conducted with nude mice into which tumor tissue, preferably of human origin, has been transplanted ("xenografted"), as is well known in this field. Test compounds are evaluated for their anti-tumor efficacy following administration to the xenograft-bearing mice.

More specifically, human tumors which have been grown in athymic nude mice are transplanted into new recipient animals, using tumor fragments which are about 50 mg in size. The day of transplantation is designated as day 0. Six to ten days later, mice are treated with the test compounds given as an intravenous or intraperitoneal injection, in groups of 5-10 mice at each dose. Compounds were given daily for 5 days, 10 days or 15 days, at doses from 10-100 mg/kg body weight. Tumor diameters and body weights were measured twice weekly. Tumor volumes are calculated using the diameters measured with Vernier calipers, and the formula:

$$(\text{length} \times \text{width}^2)/2 = \text{mg of tumor weight}$$

Mean tumor weights are calculated for each treatment group, and T/C values determined for each group relative to the untreated control tumors.

The novel compounds of the present invention show good in vitro activity in the above mentioned assay systems and antitumor activity in the above mentioned in vivo system.

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANT:

(A) BASF Aktiengesellschaft
(B) STREET: Carl-Bosch-Strasse 38
(C) CITY: Ludwigshafen
(E) COUNTRY: Bundesrepublik Deutschland
(F) ZIP: W-6700
(G) TELEPHONE: 0621/6048526
(H) TELEFAX: 0621/6043123
(I) TELEX: 1762175170

(ii) TITLE OF INVENTION: Novel peptides, the preparation and use thereof

(iii) NUMBER OF SEQUENCES: 57

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette, 3,5 inch, 2 DD
(B) COMPUTER: IBM AT-compatible, 80286 processor
(C) OPERATING SYSTEM: MS-DOS version 5.0
(D) SOFTWARE: WordPerfect version 5.1

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Xaa Val Val Xaa Val Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Xaa Val Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Xaa Val Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Xaa Val Xaa Pro Pro Val Xaa
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(2) INFORMATION FOR SEQ ID NO: 5:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Xaa Val Xaa Pro Pro Val His
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(2) INFORMATION FOR SEQ ID NO: 6:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Xaa Xaa Xaa Pro Pro Val Trp
1 5

(2) INFORMATION FOR SEQ ID NO: 7:
(i) SEQUENCE CHARACTERISTICS:
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(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Xaa Val Xaa Pro Pro Xaa Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 8:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Xaa Val Xaa Pro Pro Ile Phe
1 5

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(D) TOPOLOGY: linear
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Xaa Val Xaa Pro Xaa Val Phe
1 5

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Xaa Val Xaa Xaa Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Xaa Val Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 12:
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(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Xaa Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 13:
(i) SEQUENCE CHARACTERISTICS:
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(D) TOPOLOGY: linear
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Xaa Ile Xaa Pro Pro Val Phe
1 5

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(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Xaa Xaa Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 15:
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(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Xaa Leu Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 16:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Xaa Val Xaa Pro Pro Phe Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 17:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Xaa Val Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 18:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Xaa Val Xaa Pro Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Xaa Val Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 20:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Xaa Xaa Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 21:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Xaa Val Xaa Xaa Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 22:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Xaa Val Xaa Pro Xaa Val
1 5

(2) INFORMATION FOR SEQ ID NO: 23:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Xaa Val Xaa Xaa
1

(2) INFORMATION FOR SEQ ID NO: 24:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Xaa Xaa Xaa Pro Pro
1 5

(2) INFORMATION FOR SEQ ID NO: 25:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Xaa Xaa Pro Pro
1

(2) INFORMATION FOR SEQ ID NO: 26:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Xaa Val Xaa Pro
1

(2) INFORMATION FOR SEQ ID NO: 27:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Xaa Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Xaa Val Xaa Pro Pro Val Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 29:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Xaa Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 30:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Xaa Val Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 31:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Xaa Val Pro Pro
1

(2) INFORMATION FOR SEQ ID NO: 32:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Xaa Xaa Pro Xaa
1

(2) INFORMATION FOR SEQ ID NO: 33:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Xaa Val Xaa Pro Xaa Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 34:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Xaa Xaa Pro Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 35:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Xaa Xaa Pro Xaa Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 36:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Xaa Val Xaa Pro Pro Phe Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 37:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Xaa Val Xaa Pro Pro Xaa Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 38:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Xaa Val Xaa Pro Pro Leu Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 39:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Xaa Val Xaa Pro Pro Ile Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 40:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Xaa Val Xaa Pro Pro Val Ala
1 5

(2) INFORMATION FOR SEQ ID NO: 41:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Xaa Xaa Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 42:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Xaa Xaa Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 43:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Xaa Val Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 44:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Xaa Val Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 45:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Xaa Ile Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 46:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Xaa Val Xaa Pro Xaa Val
1 5

(2) INFORMATION FOR SEQ ID NO: 47:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Xaa Val Xaa Pro Xaa Leu Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 48:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Xaa Val Xaa Pro Xaa Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 49:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Xaa Leu Xaa Pro Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 50:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Xaa Leu Xaa Pro Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 51:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Xaa Lys Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 52:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Xaa Lys Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 53:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Xaa Lys Xaa Pro Pro
1 5

(2) INFORMATION FOR SEQ ID NO: 54:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Xaa Lys Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 55:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Xaa Xaa Xaa Pro Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO: 56:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

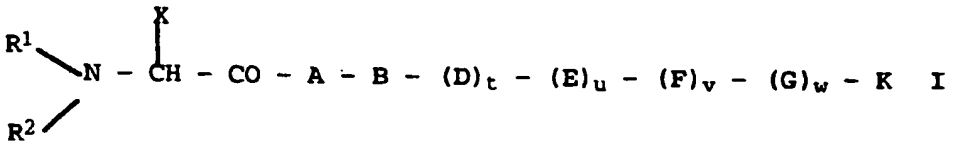
Xaa Xaa Xaa Pro Pro Val Phe
1 5

(2) INFORMATION FOR SEQ ID NO: 57:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Xaa Val Xaa Pro Pro Val Lys
1 5 --.

We claim:

1. A peptide of the formula I



I

where

R^1 is alkoxy; alkyl; cycloalkyl; alkylsulfonyl; fluoroalkyl; trifluoroacetyl; amidino; ureyl; piperidinosulfonyl; morpholinosulfonyl; benzyloxycarbonyl; alkyloxycarbonyl; aminosulfonyl which may be substituted by alkyl; hydroxy; arylsulfonyl which may be substituted by one or more substituents independently selected from alkyl, $-N(CH_3)_2$, nitro, halogen and CF_3; benzyl which may be substituted by up to three substituents independently selected from alkyl, alkoxy, nitro, halogen and CF_3; or NR^3R^4 where R^3 and R^4 may each be either hydrogen or alkyl;

R^2 is hydrogen; alkyl; fluoroalkyl; cycloalkyl; acyl; benzoyl or benzyl which may both be substituted by up to three substituents independently selected from nitro, halogen, CF_3, alkyl and alkoxy

R^1-N-R^2 together may be phthalimido, a 5- or 6-membered heterocycle which may be unsubstituted or substituted with one or more substituents independently selected from phenyl, benzyl, alkyl, $N(CH_3)_2$, nitro, thienyl, $CONH_2$ and COOEt

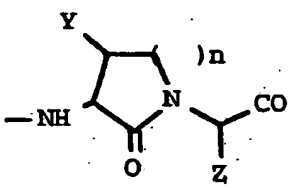
A is a valyl, isoleucyl, leucyl, allo-isoleucyl, α-aminoisobutanoyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2,4-diaminobutanoyl, ornithyl, lysyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl, norvalyl or arginyl residue;

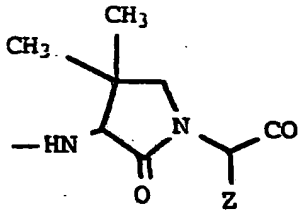
B is a N-alkyl-valyl, -norvalyl, -leucyl; -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -3-cyclohexylalanyl, -phenylalanyl, or -2-cyclohexylglycyl residue;

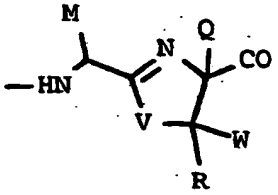
D,E,F and G are independently selected from the group consisting of prolyl, homo-prolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methyl-phenylalanyl, tetrahydroisoquinolyl-2-carbonyl, 3-thiazolylalanyl, 3-thienylalanyl, histidyl, 1-aminoindyl-1-carbonyl, 2,4-diaminobutanoyl, arginyl, 3-pyridylalanyl, 3-tert-butylalanyl, 2-cyclohexylglycyl, lysyl, norvalyl, norleucyl and 3-naphthylalanyl residues

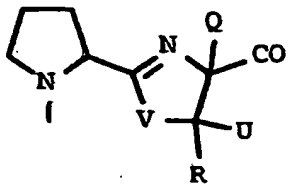
X is hydrogen, alkyl, cycloalkyl, $-CH_2$-cyclohexyl or arylalkyl

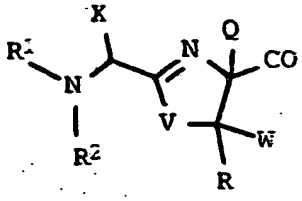
A and B together, F and G together, R^1R^2N-CHX-CO and A together, E and F together, either alone or in pairs, may be











where Y is hydrogen or lower alkyl; Z is hydrogen or lower alkyl; n is 1, 2, or 3; V is oxygen or sulfur; M is hydrogen, lower alkyl, arylalkyl, cyclohexyl, or $-CH_2$-cyclohexyl; Q is hydrogen; R is hydrogen or lower alkyl; or R and Q may together form a bond; U is hydrogen, lower alkyl, phenyl, or cycloalkyl; and W is hydrogen, lower alkyl or phenyl;

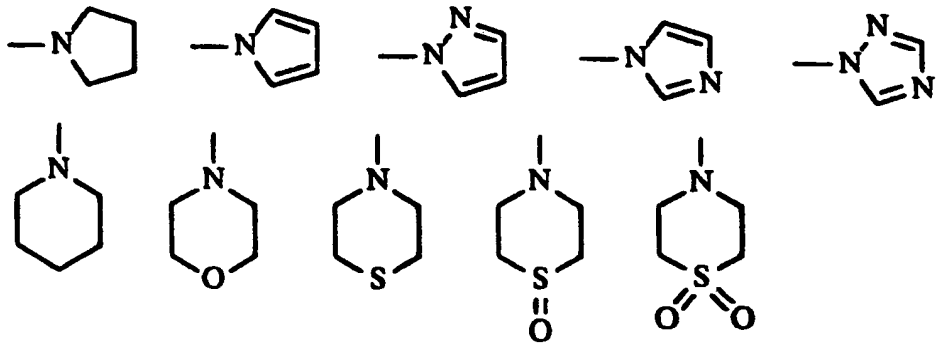
t,u,v,and w are independently 0 or 1; and

K is hydroxy, alkoxy, phenoxy, benzyloxy or a substituted or unsubstituted amino moiety;

provided that where t, u, v and w are 0, K is not a hydroxy, alkoxy, benzoxy or phenoxy moiety; and further provided that where t, u and v are 0, K is not a hydroxy or alkoxy moiety;

and the salts thereof with physiologically tolerated acids.

2. Compounds of formula I according to claim 1 wherein R^1-N-R^2 is phthalimido or a 5- or 6-membered heterocycle of the formula



which may be unsubstituted or substituted with one or more substituents which may independently be selected from phenyl, benzyl, alkyl, $N(CH_3)_2$, nitro, thienyl, oxo, $CONH_2$ and COOEt;

3. Compounds of formula I according to claim 1 wherein K is an amino moiety of the formula R^5-N-R^6 wherein

R^5 is hydrogen, or hydroxy, or C_{1-7}-alkoxy, or benzyloxy, or C_{1-7}-alkyl, or fluoroalkyl, or C_{3-7}-cycloalkyl, or benzyl which may be substituted by up to three substituents

which may independently be CF_3, nitro, C_{1-7}-alkylsulfonyl, C_{1-4}-alkoxy, phenoxy, benzoxy, halogen or C_{1-4}-alkyl

R^6 is H, or C_{1-7}-alkyl, or C_{3-7}-cycloalkyl, or fluoroalkyl, or phenyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl which may form a cyclic system, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl which may form a cyclic system, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
naphthyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, benzoxy, phenoxy, or C_{1-7}-alkyl-sulfonyl), or
benzhydryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
biphenyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
triphenylmethyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzhydrylethyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
benzhydrylmethyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
naphthylmethyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
acenaphthyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or
acenaphthylmethyl (which may be substituted by up to two

substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

pyridyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

picolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

benzothiazolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

benzisothiazolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl,C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

benzopyrazolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

benzoxazolyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

fluorenyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

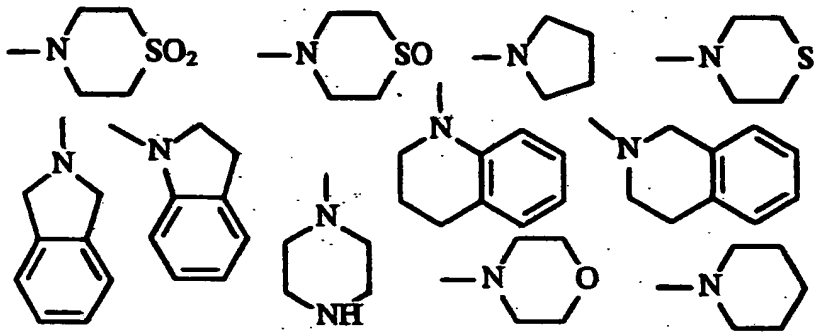
aminofluorenyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

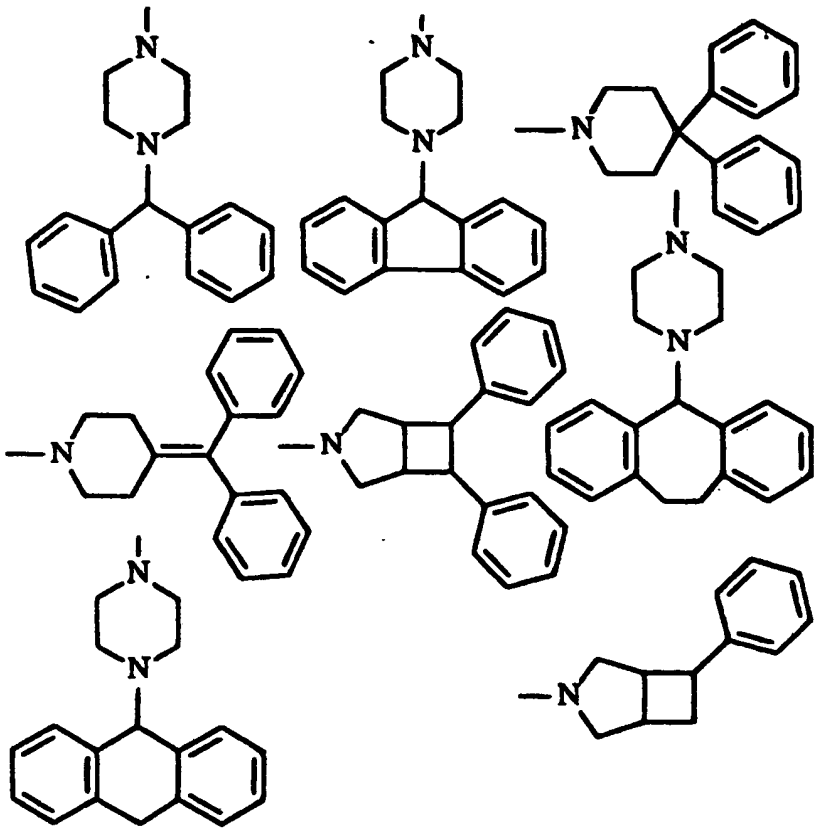
pyrimidyl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, COOEt, CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl which may form a cyclic system, C_{1-4}-alkoxy, phenoxy, benzoxy, or C_{1-7}-alkyl-sulfonyl), or

5-membered heteroaryl [which may be substituted by up to three substituents which may independently be CF_3, nitro, halogen, cyano, COOMe, COOEt, thiomethyl, thioethyl, thiophenyl, picolyl, acetyl, $-CH_2-COOEt$, $CONH_2$ CONHBzl, $CON(Bzl)_2$, C_{1-4}-alkyl which may form a cyclic system, C_{1-4}-alkoxy, phenoxy, benzoxy, phenyl (which may be substituted by up to four substituents which may indepen-

dently be nitro, CF_3, halogen, or C_{1-4}-alkyl), benzyl (which may be substituted by up to four substituents which may independently be nitro, CF_3, halogen, C_{1-4}-alkyl, naphthyl, C_{1-7}-alkyl-sulfonyl, phenylsulfonyl, or C_{1-4}-dialkylamino)], or
-CHR^7-5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, halogen, CONHBzl, $CON(Bzl)_2$, COOMe, COOEt, $COOCH(CH_3)_2$, $CONH_2$, COOBzl, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenoxy, benzoxy, phenyl, benzyl, naphthyl, or C_{1-7}-alkyl-sulfonyl [R^7 = H, linear or branched C_{1-5}-alkyl, benzyl; or R^7 and R^5 together form a group $-(CH_2)_3-$ or $-(CH_2)_4-$]).

4. Compounds of formula I according to claim 1 wherein K is R^5-N-R^6 which together may form structures selected from the group consisting of





which may be unsubstituted or substituted with one or more substituents independently selected from the group consisting of CF_3, nitro, halogen, oxo, cyano, N,N-dimethylamino, CONHBzl, $CON(Bzl)_2$, C_{1-6}-alkyl, C_{3-4}-alkylen group forming an annelated ring system, C_{1-4}-alkoxy, phenoxy, benzoxy, naphthyl, pyrimidyl, COOEt, COOBzl, C_{3-6}-cycloalkyl, pyrolidinyl, piperidinyl, thienyl, pyrolyl, $-CH_2-CO-NCH(CH_3)_2$, $-CH_2-CO-N(CH_2)_4$, $-CH_2-CO-N(CH_2)_4O$, benzyl (which may be substituted by up to three substituents independently selected from the group consisting of nitro, halogen, CF_3, thiomethyl or the corresponding sulfoxide or sulfone, thioethyl or the corresponding sulfoxide or sulfone, C_{1-4}-alkyl, and C_{1-4}-alkoxy), and phenyl (which may be substituted by up to three substituents independently selected from the group consisting of nitro, halogen, CF_3, thiomethyl, thioethyl, C_{1-4}-alkyl, and C_{1-4}-alkoxy).

5. Compounds of formula I according to claim 1 wherein t, u, v, and w are zero and K is not an hydroxy, benzoxy, phenoxy or alkoxy moiety.

6. Compounds of formula I according to claim 1 wherein t, u, and v are zero and K is not an hydroxy or alkoxy moiety.

7. Compounds of formula I according to claim 1 wherein t, u, v and w are 1 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

8. Compounds of formula I according to claim 1 wherein t, u and v are 1, w is 0 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

9. Compounds of formula I according to claim 1 wherein t and u are 1, v and w are 0 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

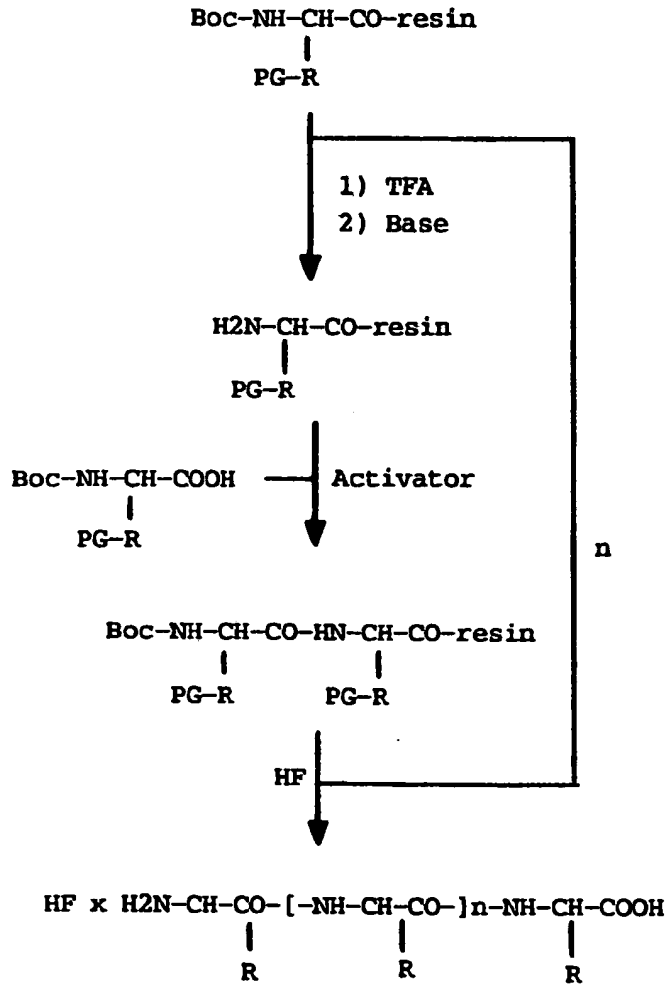
10. Compounds of formula I or salts thereof for use in medicine in particular for treating oncological diseases.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

12. A method of treating a tumor in a mammal comprising administering to a mammal bearing such a tumor, a tumor-inhibiting amount of a compound of claim 1.

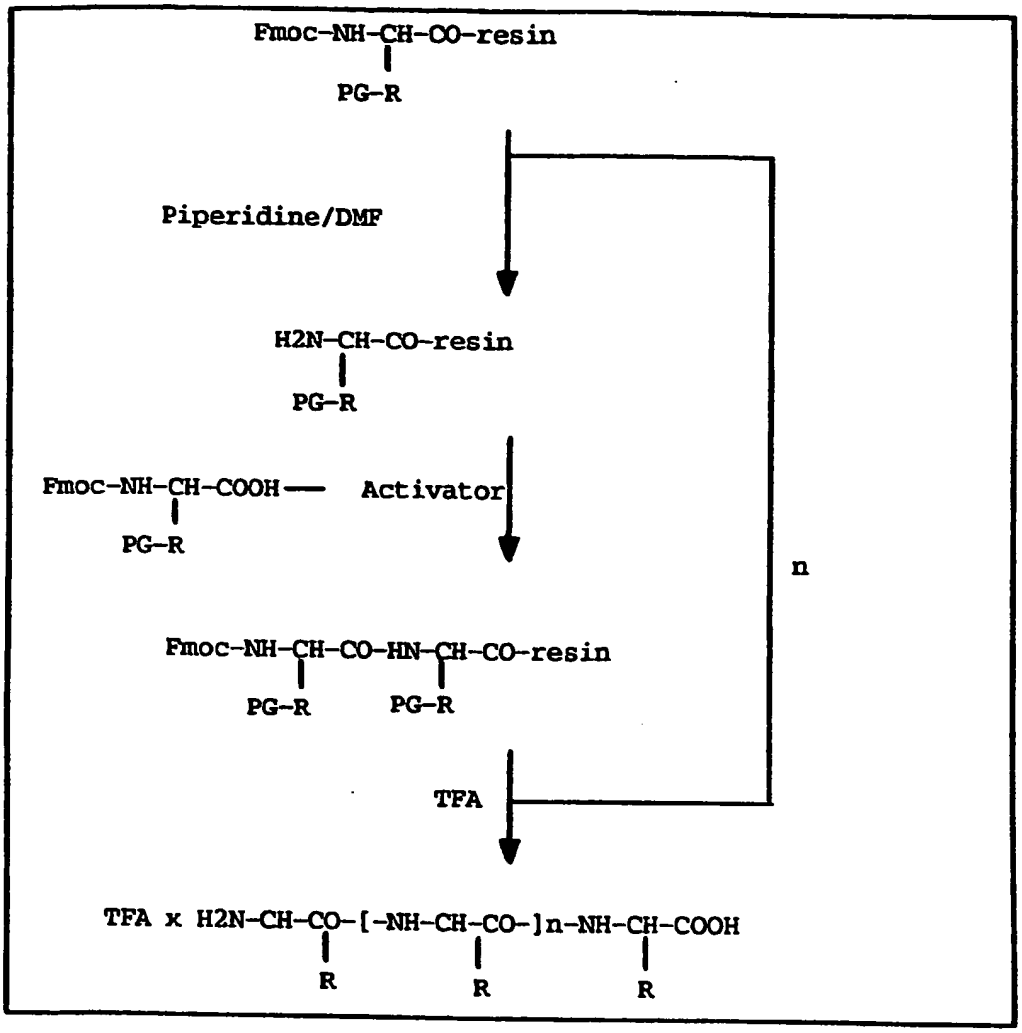
13. The method of preparing compounds of formula I according to claim 1 characterized in that they are prepared according to known methods of peptide chemistry.

Fig. 1: The Boc protective group technique on a polymeric support



Boc = t-butyloxycarbonyl protective group
PG = side-chain protective group
R = amino-acid side chain

Fig. 2: The Fmoc protective group technique on a polymeric support



Fmoc = 9-fluorenylmethyloxycarbonyl protective group
PG = side-chain protective group
R = amino-acid side chain

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01138

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K5/10; C07K7/06; A61K37/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 398 558 (ARIZONA BOARD OF REGENTS) 22 November 1990 ---	
A	J.AM.CHEM.SOC. vol. 113, 1991, pages 6692 - 6692 PETTIT, G.R. ET AL. 'Antineoplastic Agents. 220. Synthesis of Natural (-)-Dolastatin 15' ---	
A	BIOCHEMICAL PHARMACOLOGY vol. 40, no. 8, 1990, pages 1859 - 1864 BAI, R. ET AL. 'Structure-activity studies with chiral isomers and with segments of the antimitotic marine peptide dolastatin 10' -----	

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26 JULY 1993	14 -09- 1993
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HERMANN R.

INTERNATIONAL SEARCH REPORT

Internal application No.
PCT/EP 93/01138

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See annex.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The scope of the claims is speculative. A formula consisting virtually of variables which are moreover ill-defined ("heterocycle substituted with one ore more substituents...") is hardly a clear and concise definition of patentable subject-matter, or a permissible generalisation which is fairly based on experimental evidence. The search has been limited to the synthesized compounds (examples 1,2, and table on page 75).

See Arts. 5,6 and 17 (2)(a)iiPCT.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301138
SA 73653

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 26/07/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0398558	22-11-90	US-A- 4879278	07-11-89
		CA-A- 2012480	16-11-90
		JP-A- 2311496	27-12-90

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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